

# Norepinephrine

---

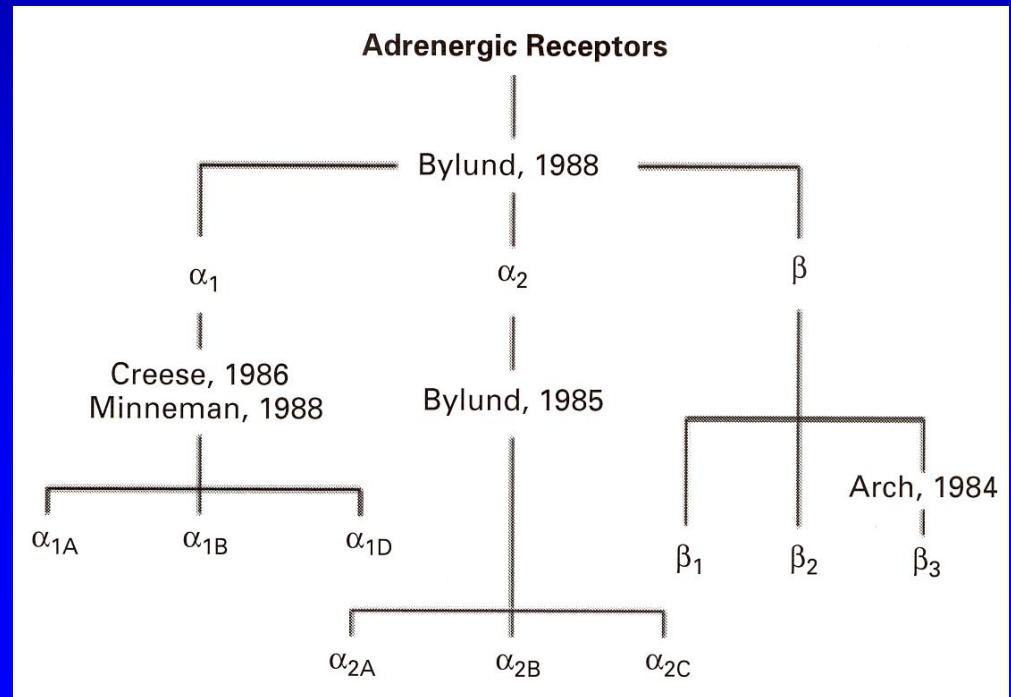
# Norepinephrine receptors

- $\alpha$  family
- B family

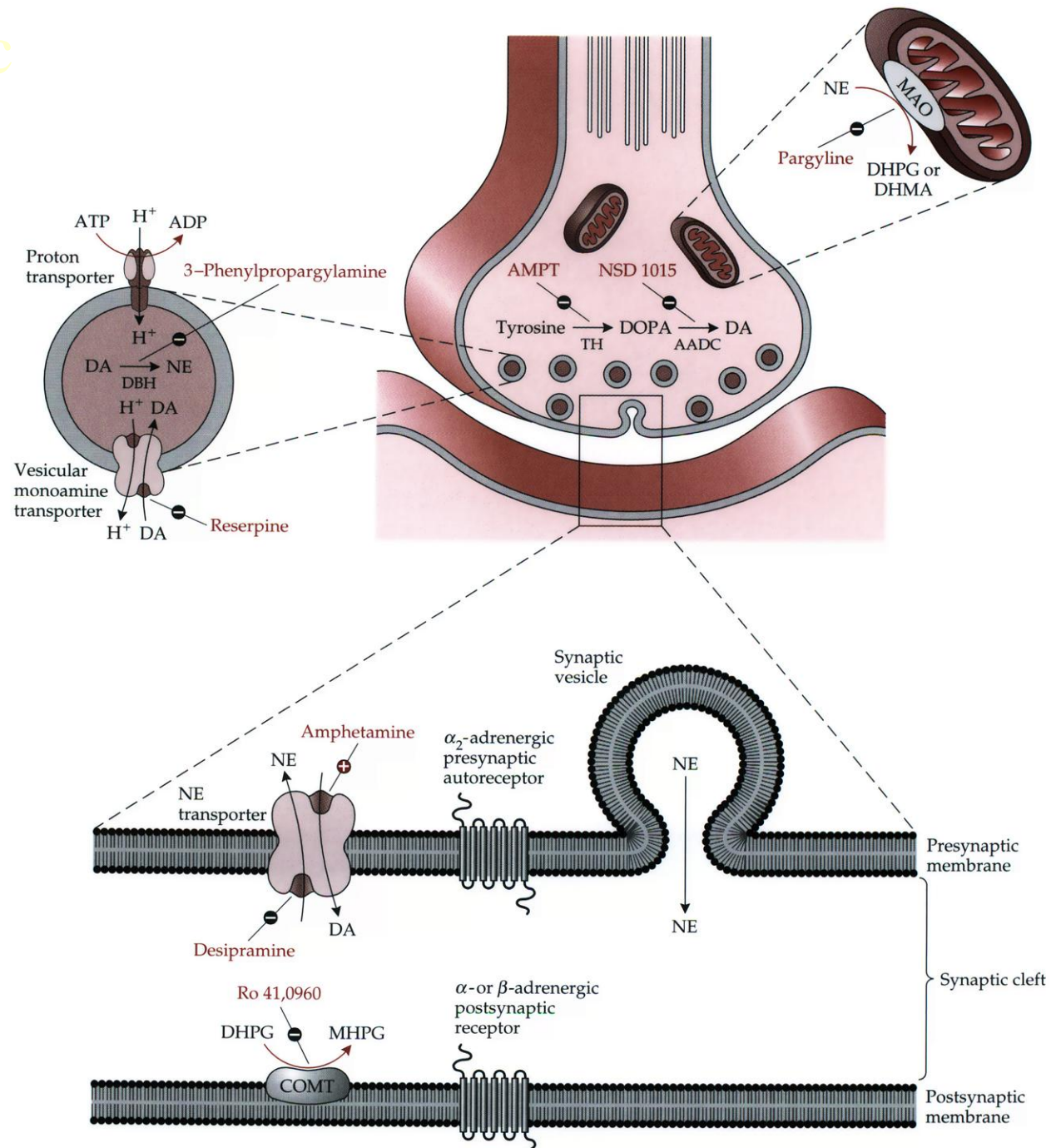
# Norepinephrine receptors

- $\alpha$  family
- $\beta$  family

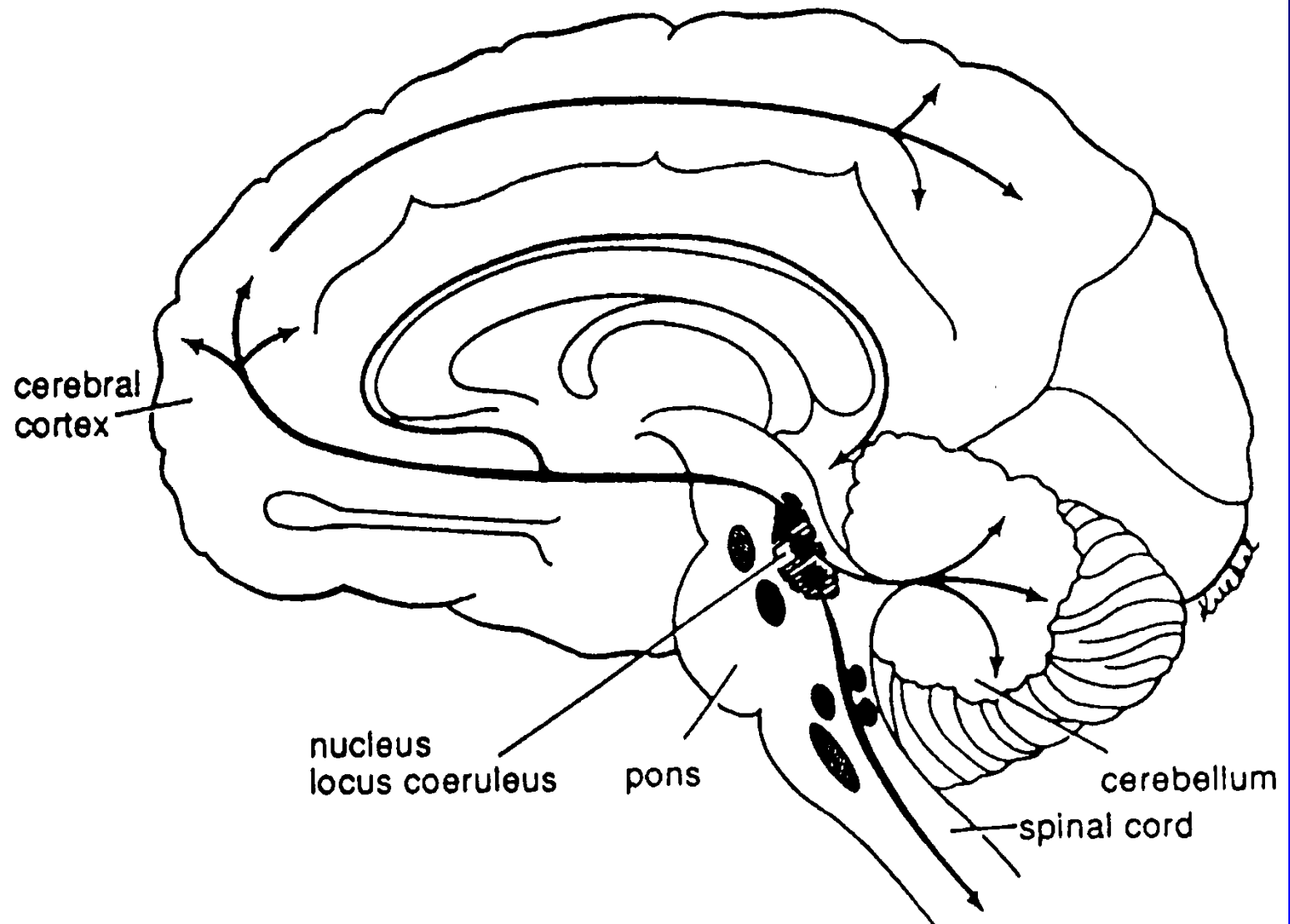
## Current Nomenclature of Adrenergic Receptor Subtypes



# Noradrenergic (NE) synapse



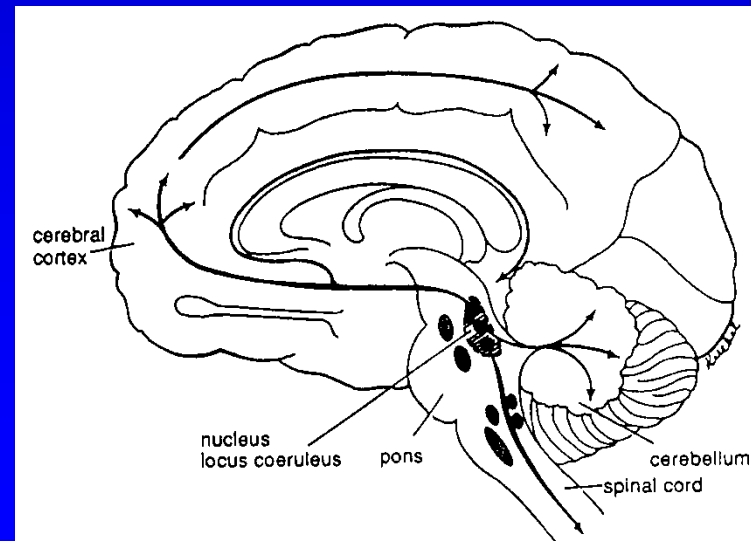
# Norepinephrine Pathway



# Norepinephrine Pathway

---

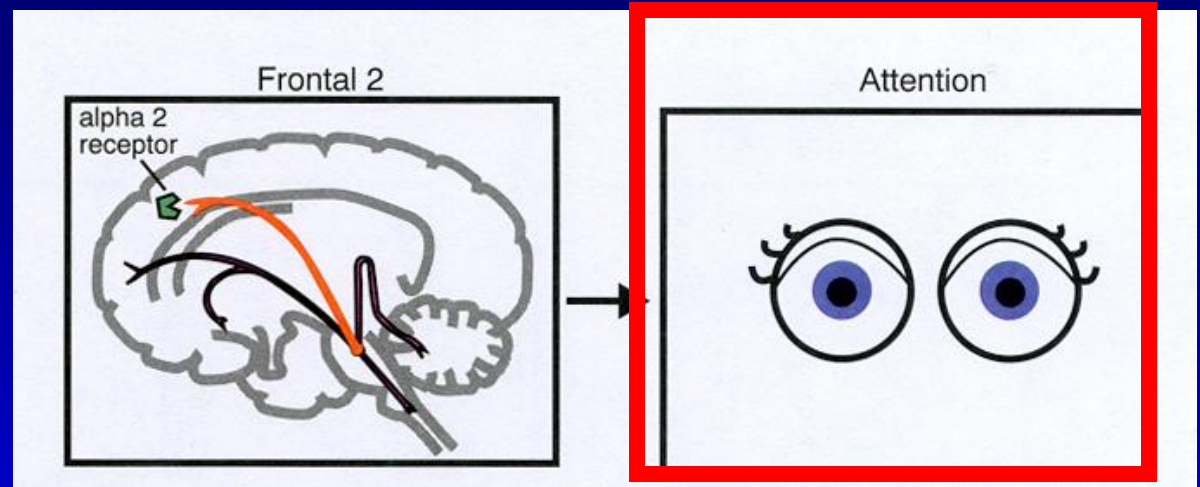
- LC noradrenergic system is highly responsive external stimuli → attention
- Learning/memory and sleep/wake cycle
- Anxiety and stress response
- In FRONTAL CORTEX:
  - Mood regulation → Hypofunction of pathway → Depression



# NE: Locus Ceruleus → FRONTAL CTX

$\alpha 2$  postsynaptic receptor  
In FRONTAL CORTEX:

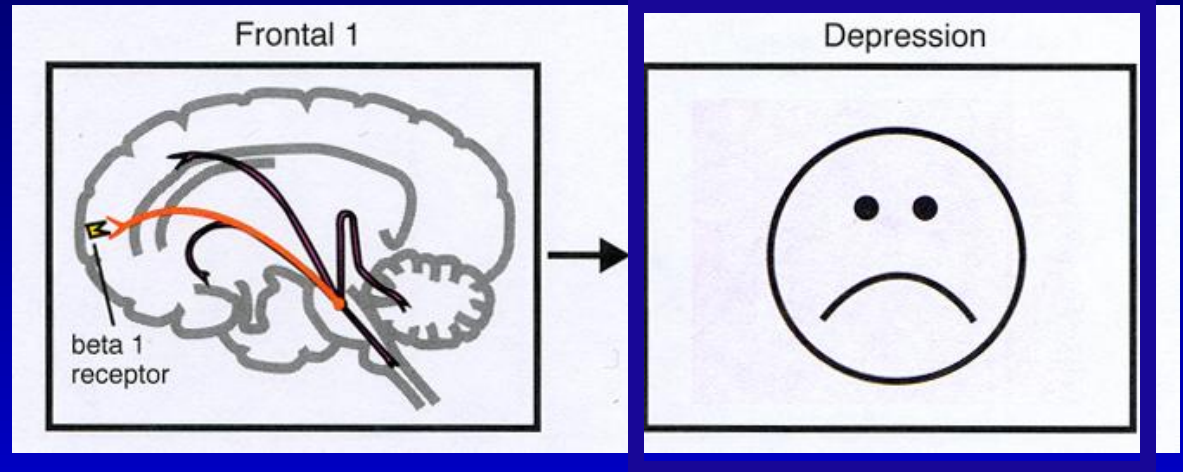
- **Attention**, working memory, information processing.



# NE: Locus Ceruleus → FRONTAL CTX



$\beta 1$  postsynaptic receptor  
In FRONTAL CORTEX:

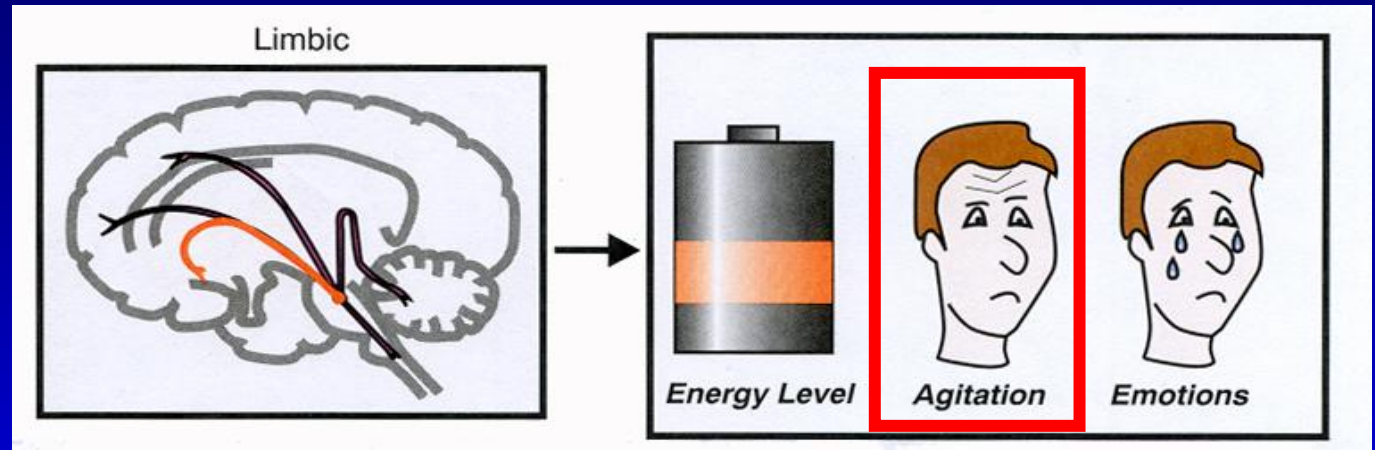
- Mood regulation.
- **Hypofunction** of pathway:
  - Depression





# NE: Locus Ceruleus → LIMBIC CTX

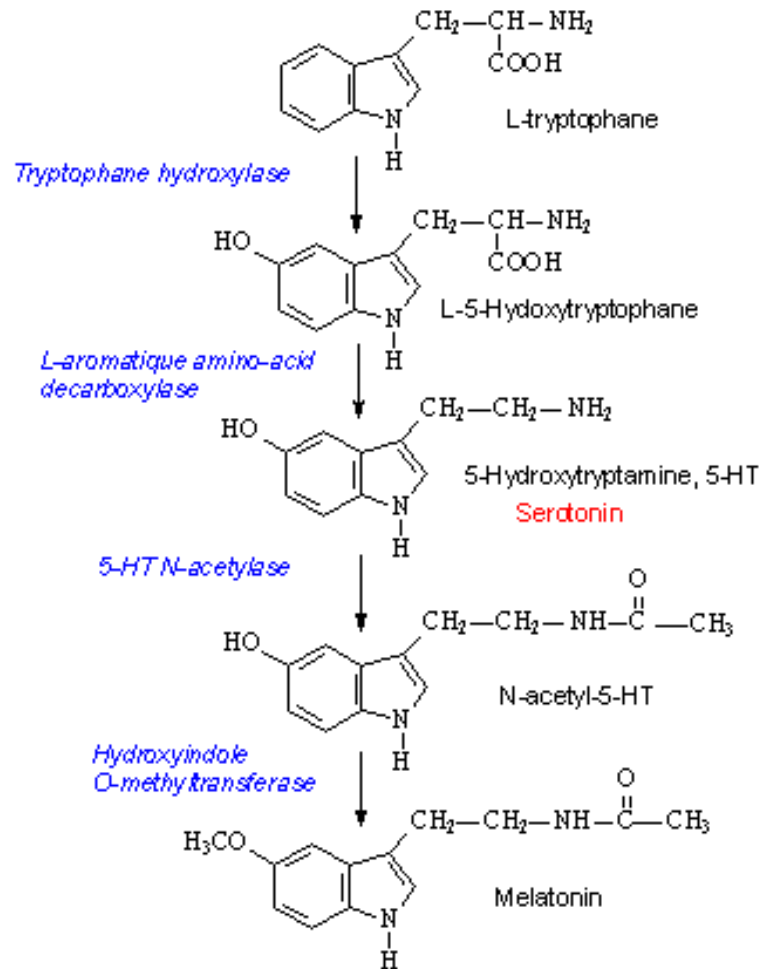
- Emotions
- Energy level
-  **Psychomotor agitation**
-  **Psychomotor retardation**



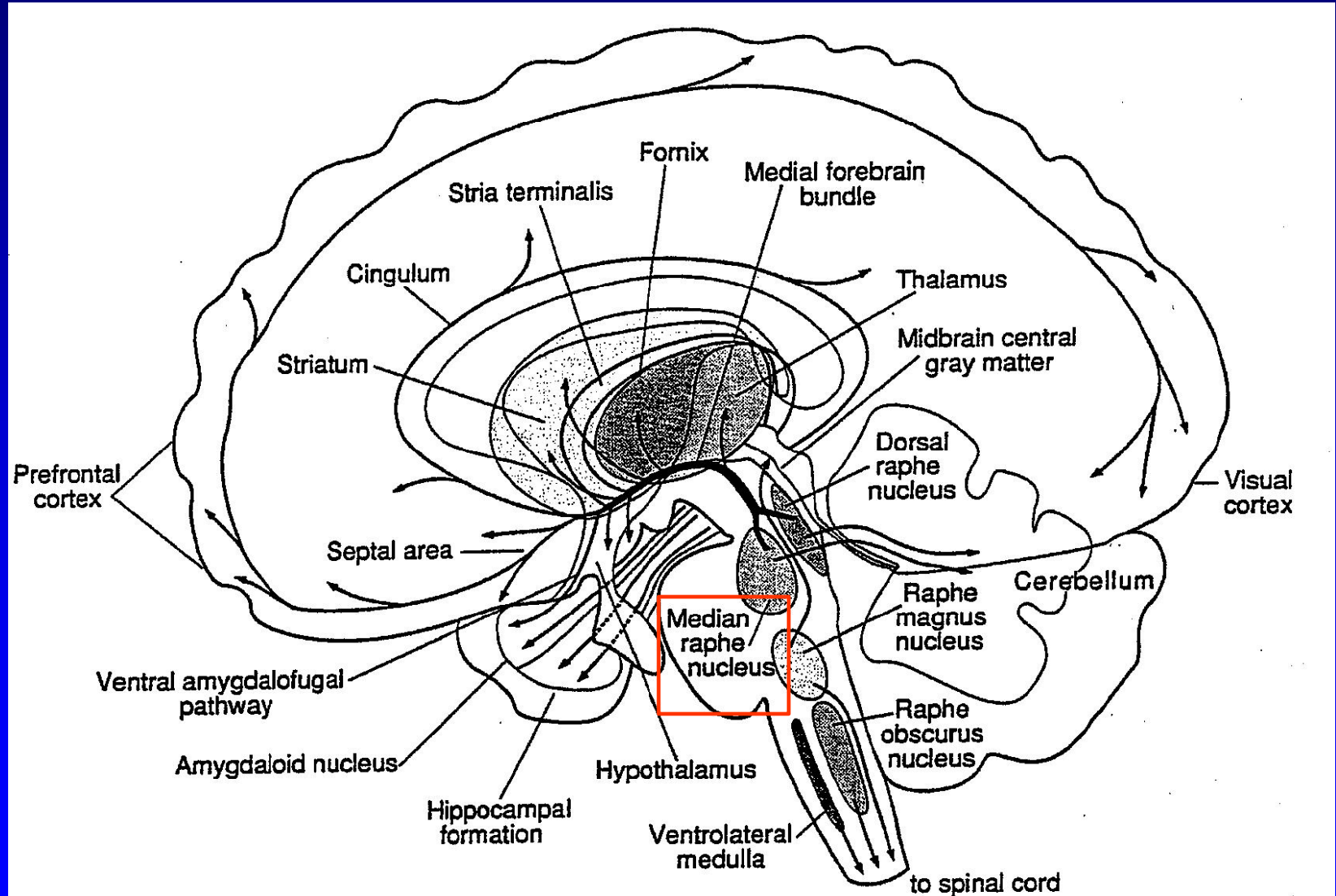
# Serotonin

---

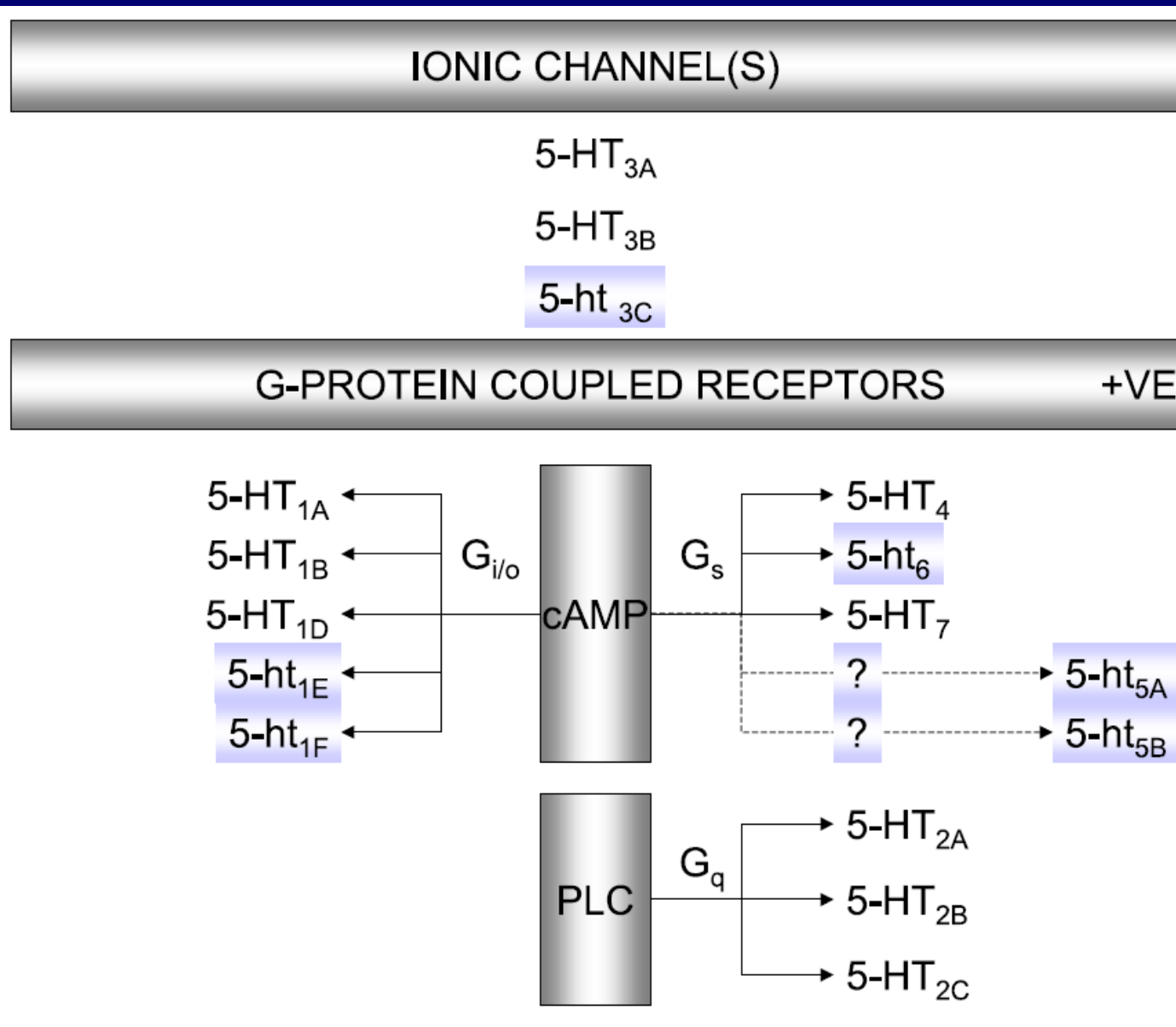
# Serotonin synthesis



# Serotonin Pathway

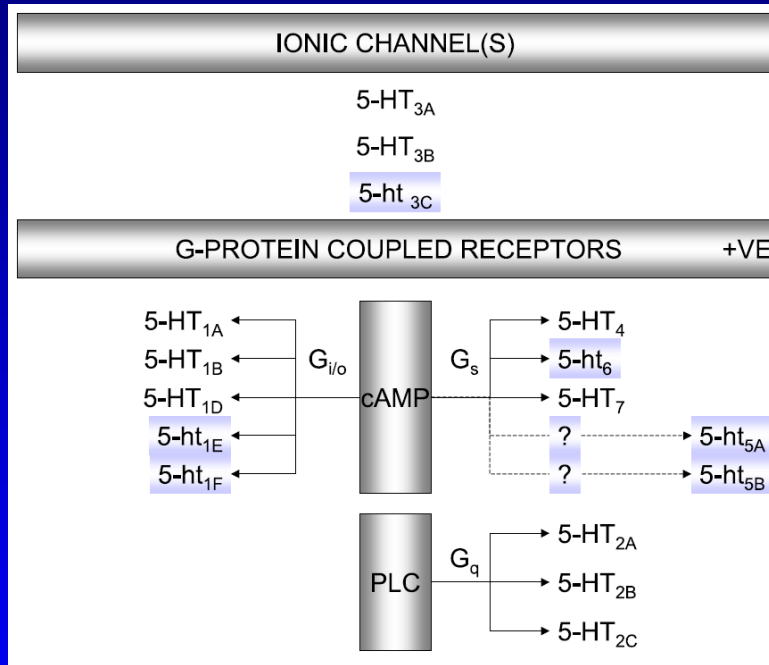


# Serotonin Receptors

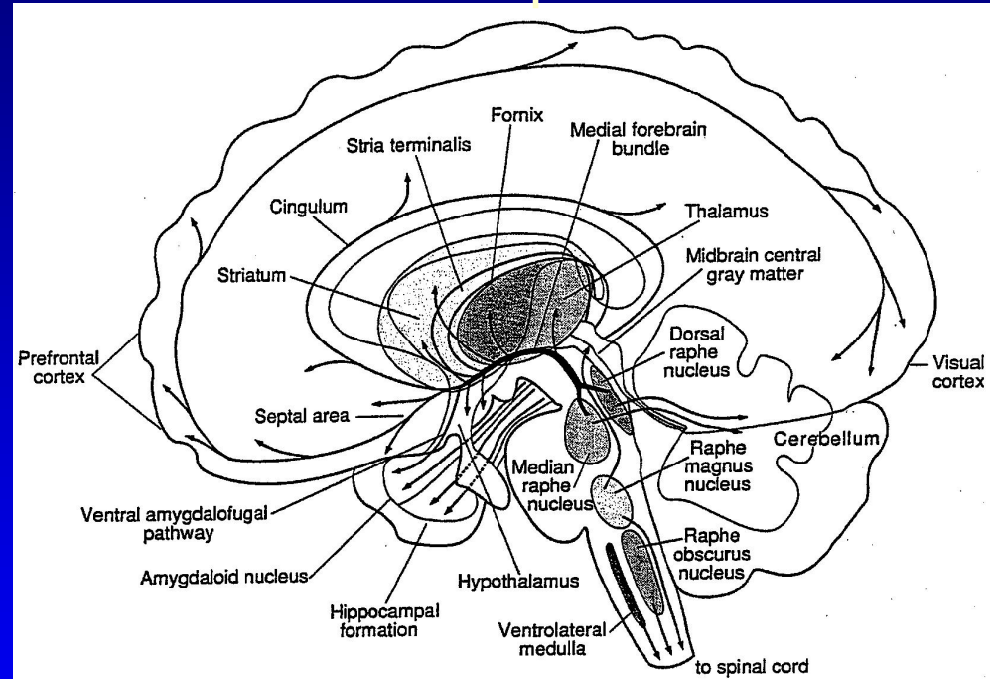


# Serotonin Pathway

Almost 17 type of receptor

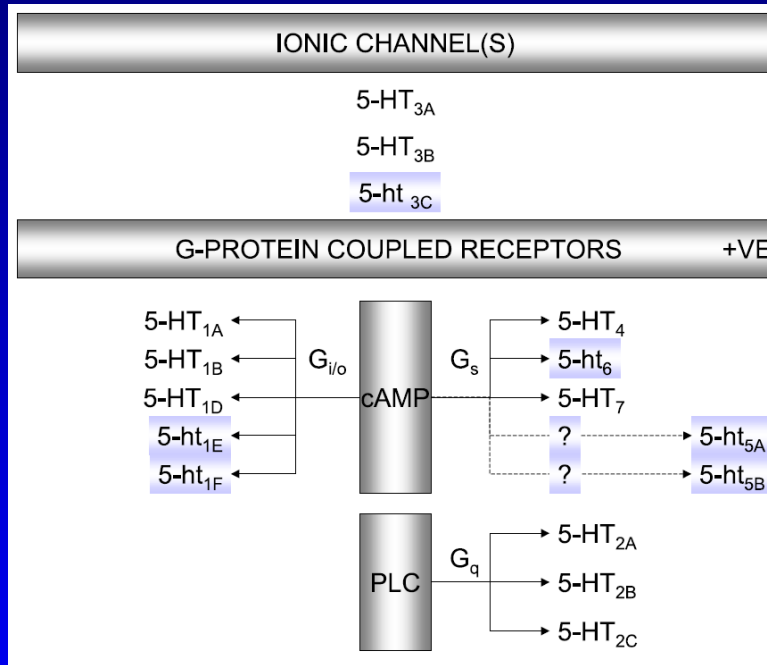


Wide spread

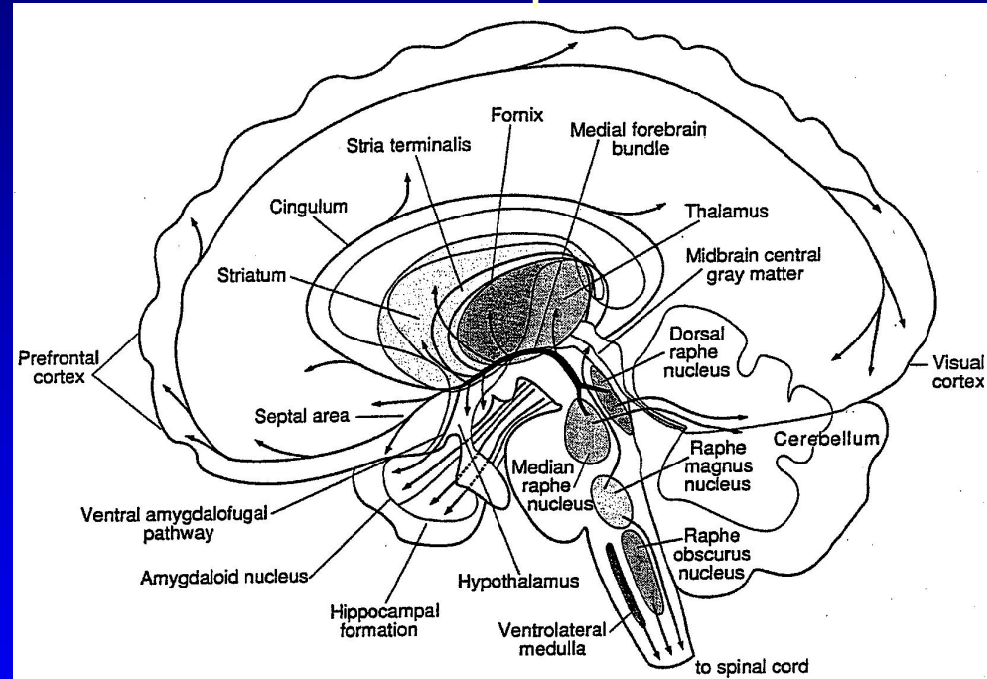


# Serotonin Pathway

Almost 17 type of receptor



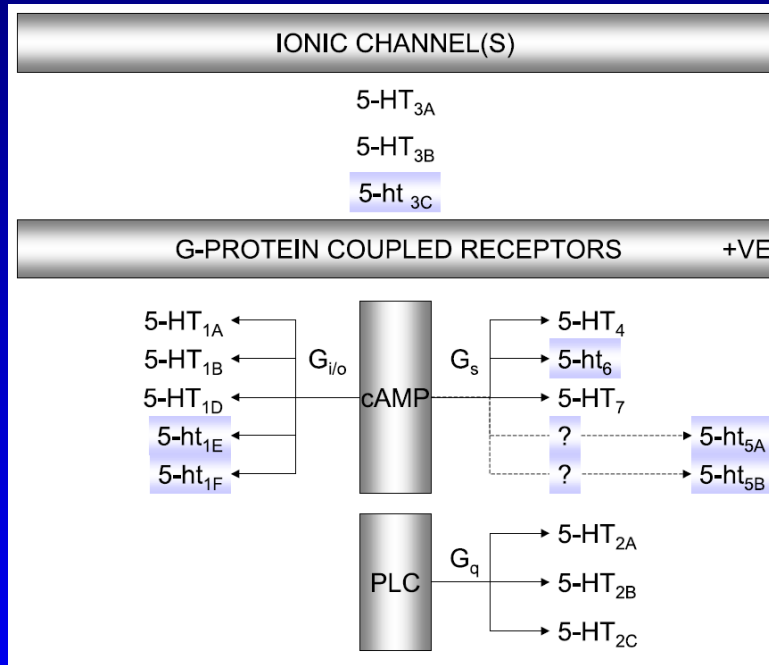
Wide spread



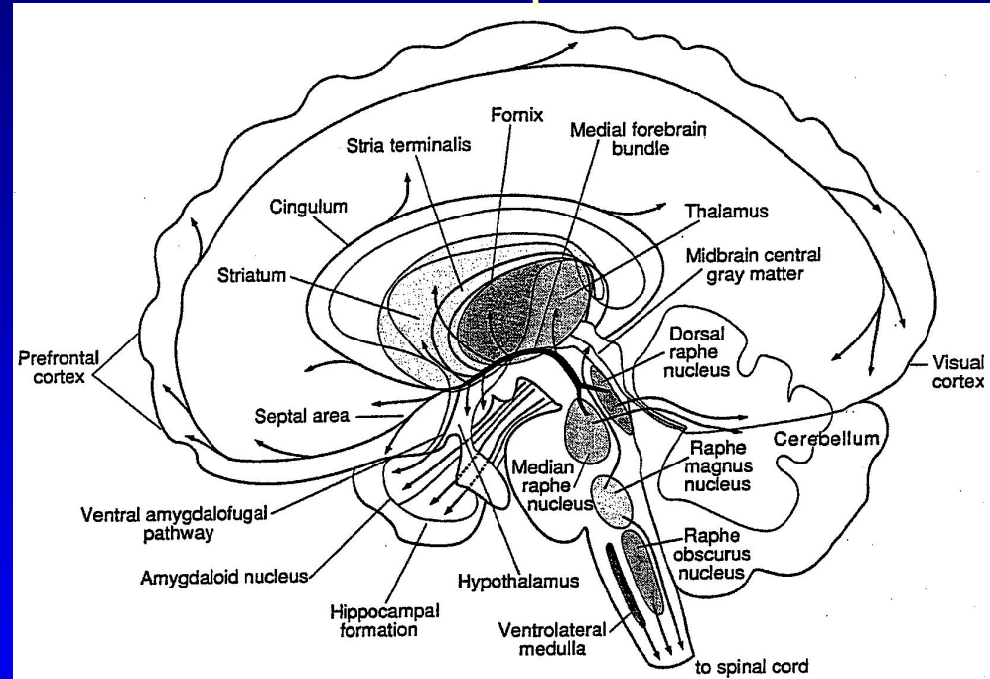
mood, sleep, sexuality, impulsivity, aggression, stress, drug abuse

# Serotonin Pathway

Almost 17 type of receptor



Wide spread



Serotonin system *dysfunction* involve in :  
 Depression, Schizophrenia,  
 OCD, Eating Disorders, Autism



## Antipsychotics

Clozapine  
Risperidone  
Olanzapine



Potent antagonist actions at  
5-HT<sub>2A</sub> receptors, in addition  
to D<sub>2</sub> antagonism

## Anxiolytics

Buspirone  
Gepirone



Partial 5-HT<sub>1A</sub> agonists  
Effective for treating GAD, OCD

## Antiemetics

Ondansetron  
Granisetron



5-HT<sub>3</sub> antagonist used for  
Minimizing chemotherapy-  
induce nausea

## Anti-migraine

Sumatriptan

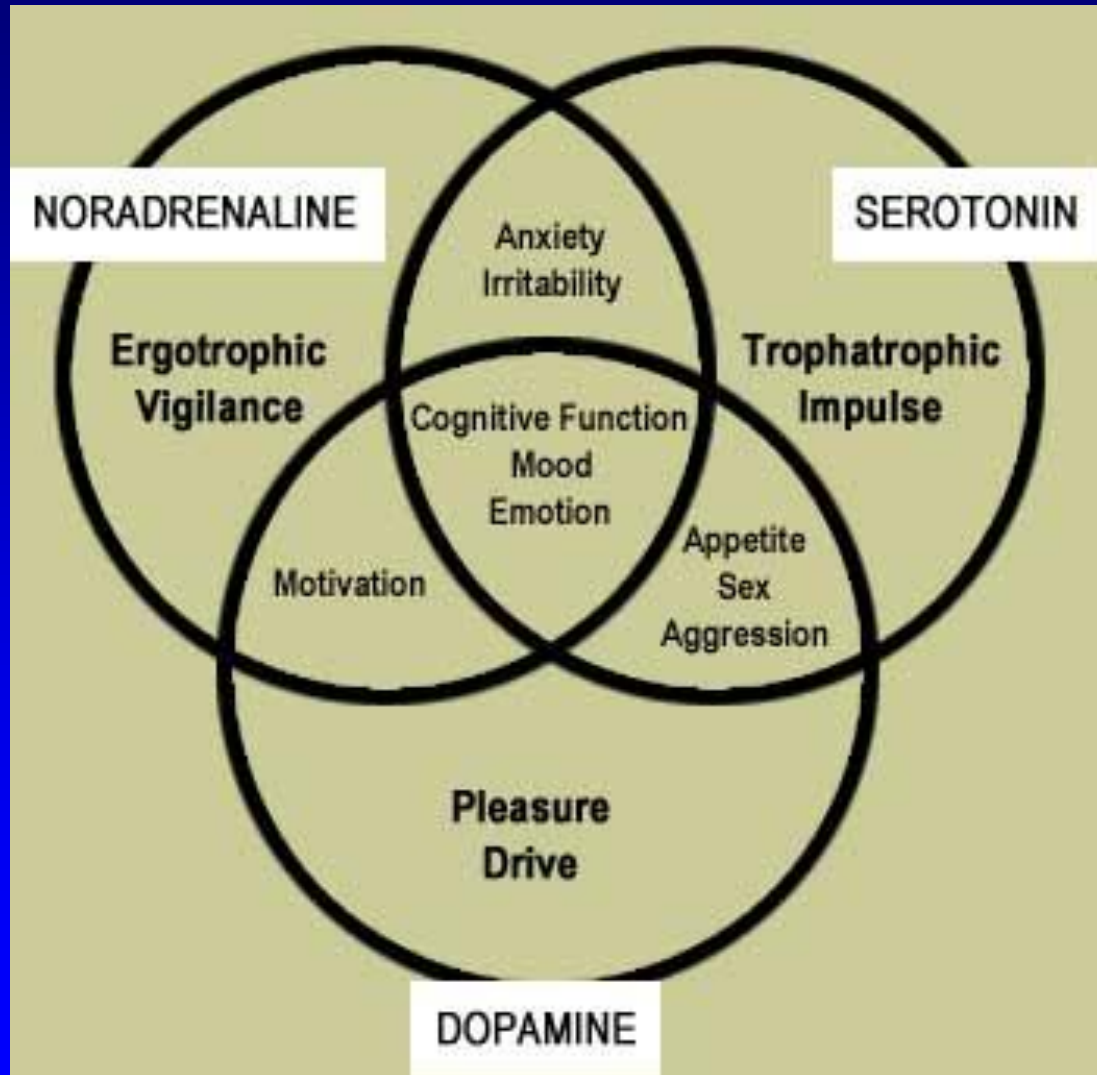


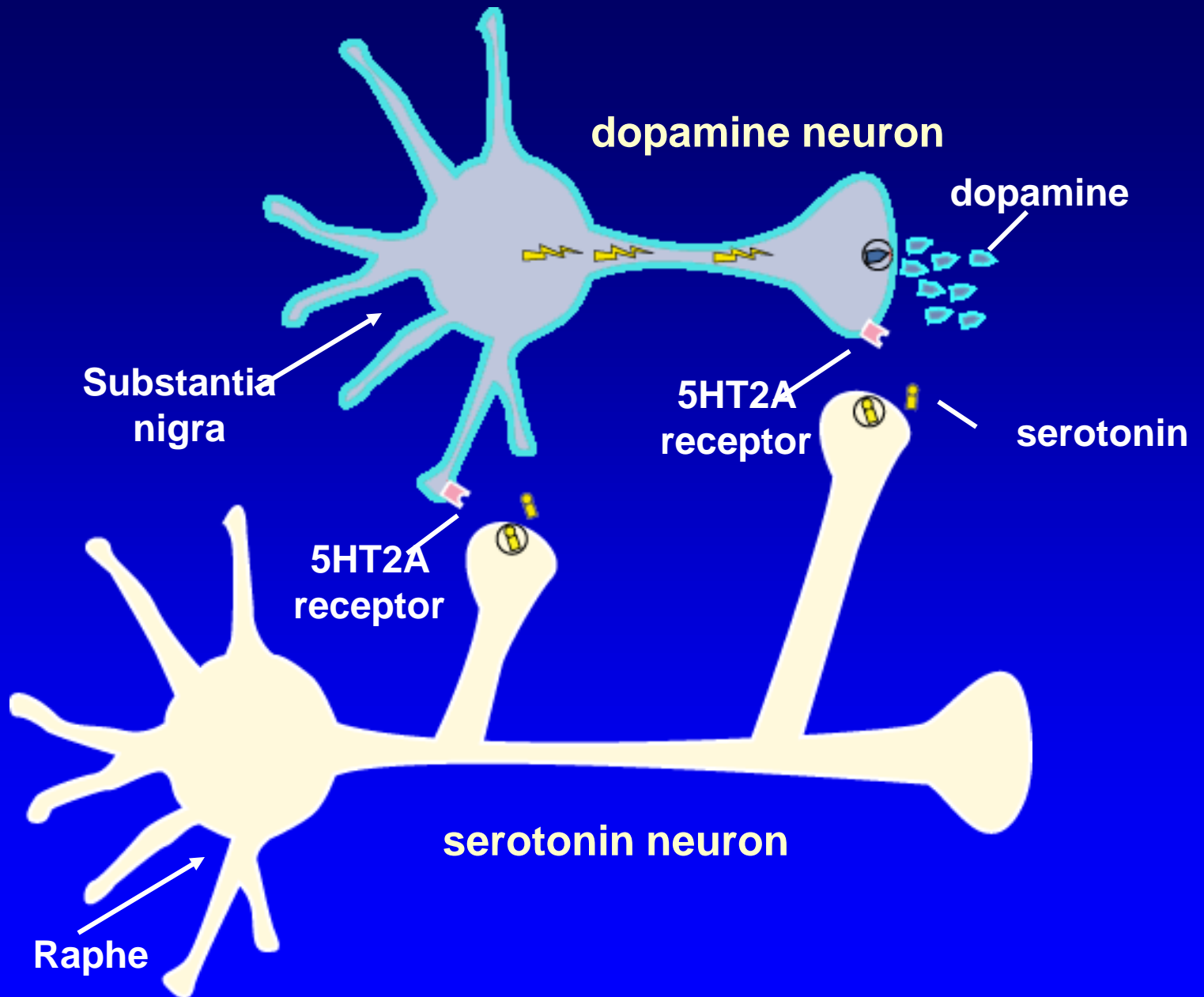
5-HT<sub>1</sub> agonist, exerts some  
Selectivity on 5-HT<sub>1D</sub> receptors

# Selective Serotonin Reuptake Inhibitors



# Monoamines & Behavior





# Neuropeptides

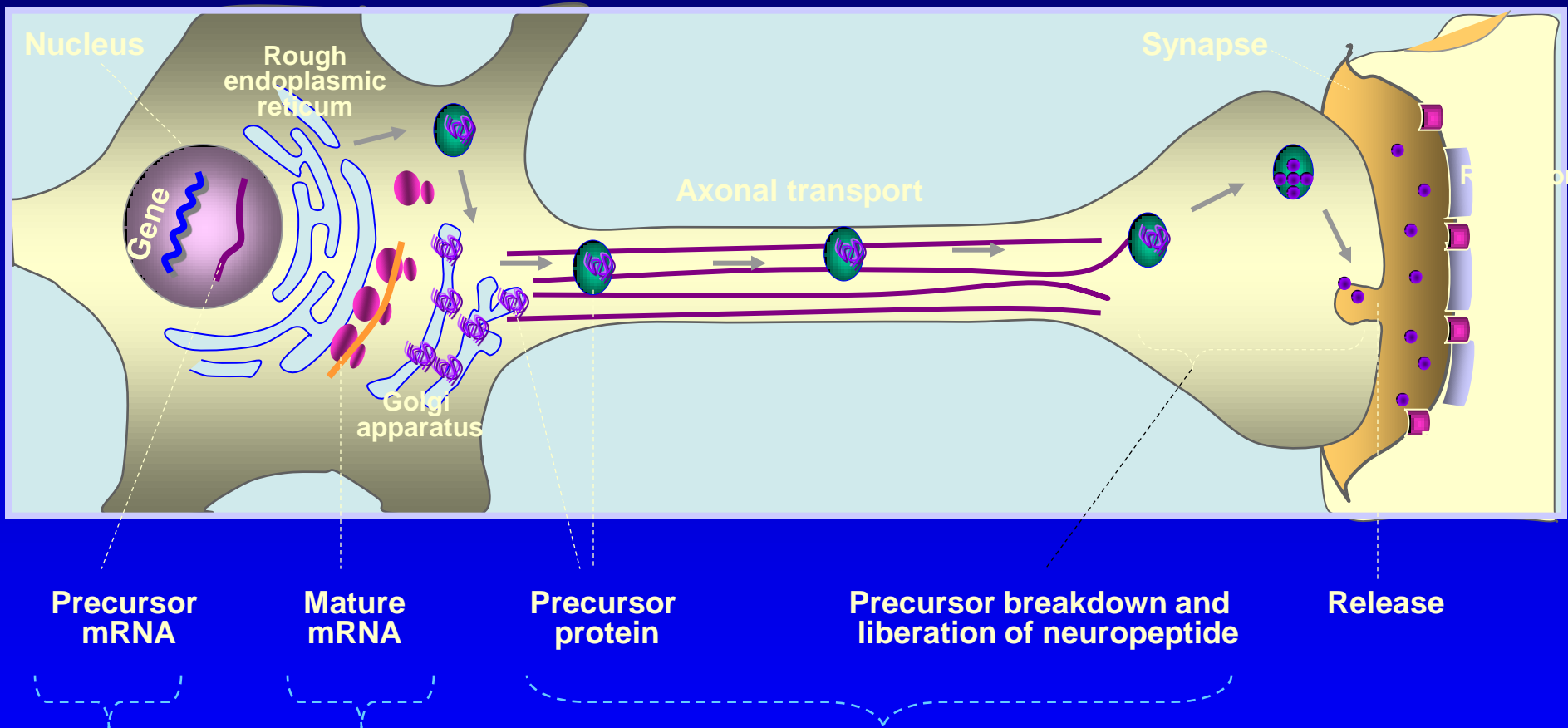
---

# Neuropeptides

---

- **Neuropeptides are peptides released by neurons as intercellular messengers.**
- **May co-localize with other classical transmitters in same neuron**
- **All neuropeptide receptors are G-protein linked receptors**
- **Function of Neuropeptides:**
  - **-- They can do just about everything**

# Neuropeptides synthesis



Usually are more potent than classical neurotransmitter : lower concentration and longer effect

# PAIN



- Pain from poena ---> Latin means **punishment**



# **PAIN - INTRODUCTION**

- **Pain is the most important protective sensation.**
- **It is an unpleasant sensation and is the most primitive of all senses.**
- **It is the feeling of distress or suffering or agony caused by stimulation of the receptors for pain.**
- **Pain is associated with emotional component or affect, other accompaniments are arousal response, somatic and autonomic reflexes.**

# TERMINOLOGIE

TERM	DESCRIPTION
<b>ALLODYNIA</b>	PERCEPTION OF NON-NOXIOUS STIMULUS AS PAIN
<b>ANALGESIA</b>	ABSENCE OF PAIN PERCEPTION
<b>ANESTHESIA</b>	ABSENCE OF ALL SENSATIONS
<b>ANESTHESIA DOLOROSA</b>	PAIN IN AN AREA THAT LACKS SENSATION
<b>DYSESTHESIA</b>	UNPLEASANT SENSATION WITH OR WITHOUT STIMULUS
<b>HYPOALGESIA</b>	DIMINISHED RESPONSE TO NOXIOUS STIMULUS
<b>HYPERALGESIA</b>	INCREASED RESPONSE TO NOXIOUS STIMULUS
<b>HYPERASTHESIA</b>	INCREASED RESPONSE TO MILD STIMULUS
<b>HYPOASTHESIA</b>	REDUCED CUTANEOUS SENSATION
<b>NEURALGIA</b>	PAIN IN THE DISTRIBUTION OF A NERVE
<b>PARASTHESIA</b>	ABNORMAL SENSATION PERCEIVED WITHOUT AN APPARENT STIMULUS
<b>RADICULOPATHY</b>	FUNCTIONAL ABNORMALITY OF NERVE ROOTS



# TYPES OF PAIN FIBRES

TYPE OF NERVE	CONDUCTION VELOCITY ( MTS/SEC )	MELINATED	TYPE OF PAIN
A- DELTA	20 (fast)	YES	SHARP, PRICKING, WELL LOCALIZED
C	1 (slow)	No	DULL ACHE, DIFFUSE

# **TYPES OF PAIN:**

## **Fast pain/Slow pain**

- Immediately after an injury (i.e., stimulus for pain) a sharp, localised pain is felt, which is called fast pain and is carried by A-delta fibres at higher speed.
- After the fast pain, a diffuse, dull, intense and unpleasant pain sensation occurs, which is called slow pain and is carried by C fibres at slower speed.

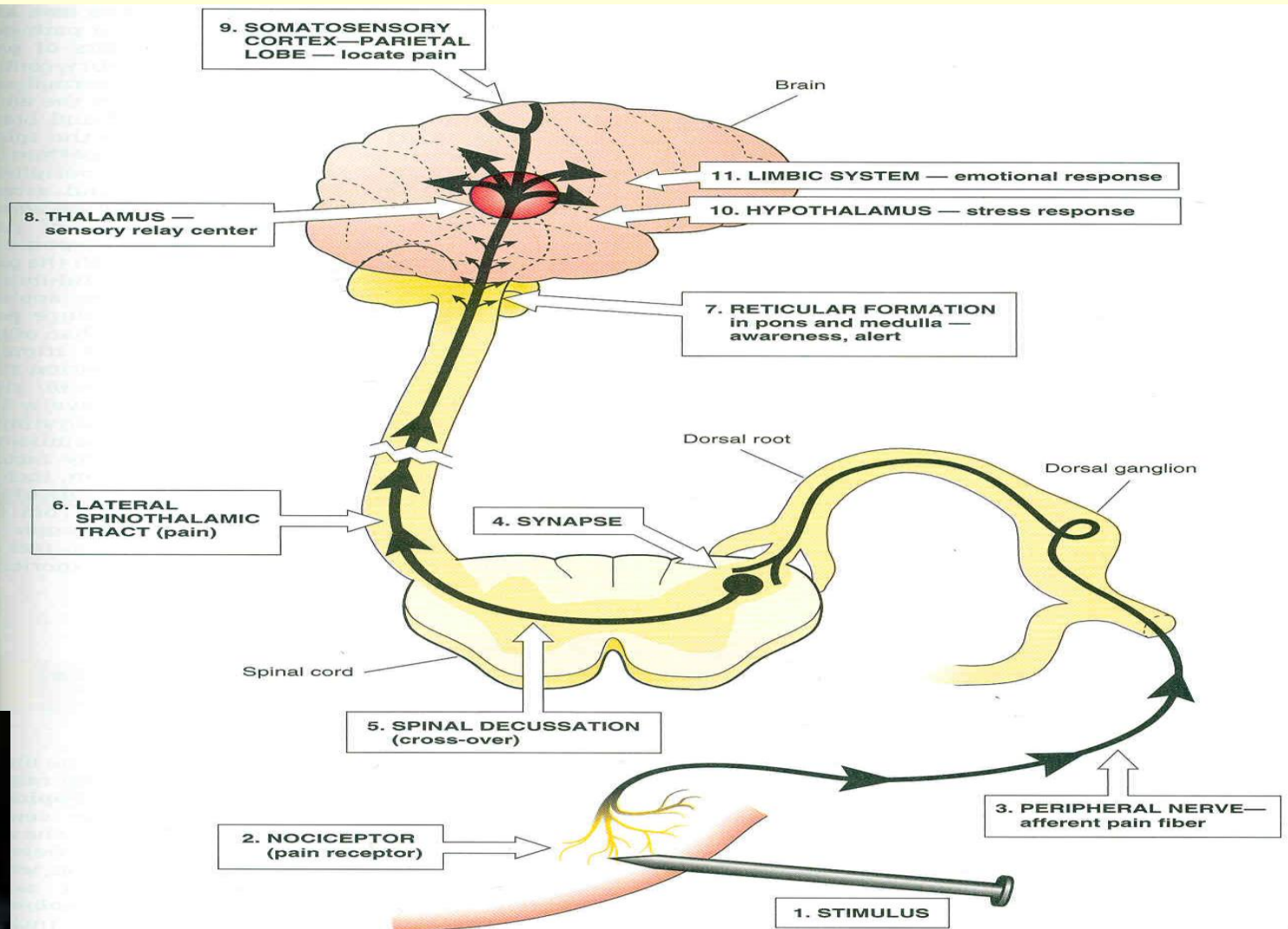


FIGURE 13-1 Pain pathway.



# PAIN PATHWAY

# **ASCENDING PATHWAYS**

- **“SPINAL LEMNISCUS” OR “ANTEROLATERAL FASCICULUS”**
- **SPINOTHALAMIC TRACT**
  - **Neospinothalamic tract**
    - **project to Thalamus**
    - **synapse and project to somatosensory cortex**
  - **Paleospinothalamic tract**
    - **to thalamus, midbrain, pontine and medullary reticular formation, periaqueductal grey and hypothalamus**
  - **Somatotopically and contralaterally organised,**
  - **Functions**
    - **mostly high threshold and multireceptive**
    - **small discriminative or whole body receptive fields**

# ASCENDING PATHWAYS

- **Spinoreticular tract**
  - projects to medullary and pontine reticular formation
  - involved in motivational and affective responses to pain
  - ascend medially to spinothalamic tract
  - also responds to non-noxious stimuli+
- **Spinomesencephalic tract**
  - project to caudal midbrain areas including periaqueductal gray

# **MID BRAIN**

- **PERIAQUECDUCTAL GRAY (PAG)**
  - surrounds cerebral aqueduct
  - extensive afferent and efferent projections
  - stimulation produce potent antinociception
- **LOCUS COERULEUS (LC)**
  - noradrenergic containing neurones
  - diffusely innervates CNS at all levels
  - descending fibres inhibit dorsal horn nociceptive activity and spinal nociceptive reflexes

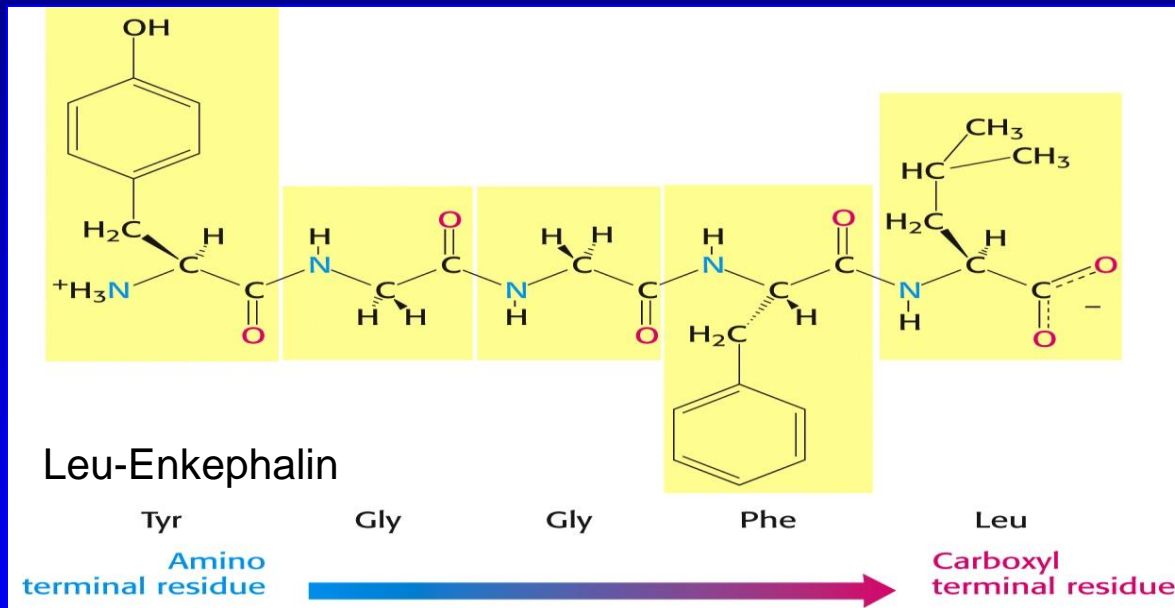


# **DESCENDING CONTROL**

- **CORTEX**
  - via corticospinal efferents
  - terminations in superficial laminae
  - may be inhibitory or excitatory and influence non-noxious stimuli as well
- **HYPOTHALAMUS**
  - many afferents and efferents - including NTS, PAG, LC, parabrachial nuclei, raphe nuclei
  - widespread reciprocal innervation
  - may be relay for descending inhibition

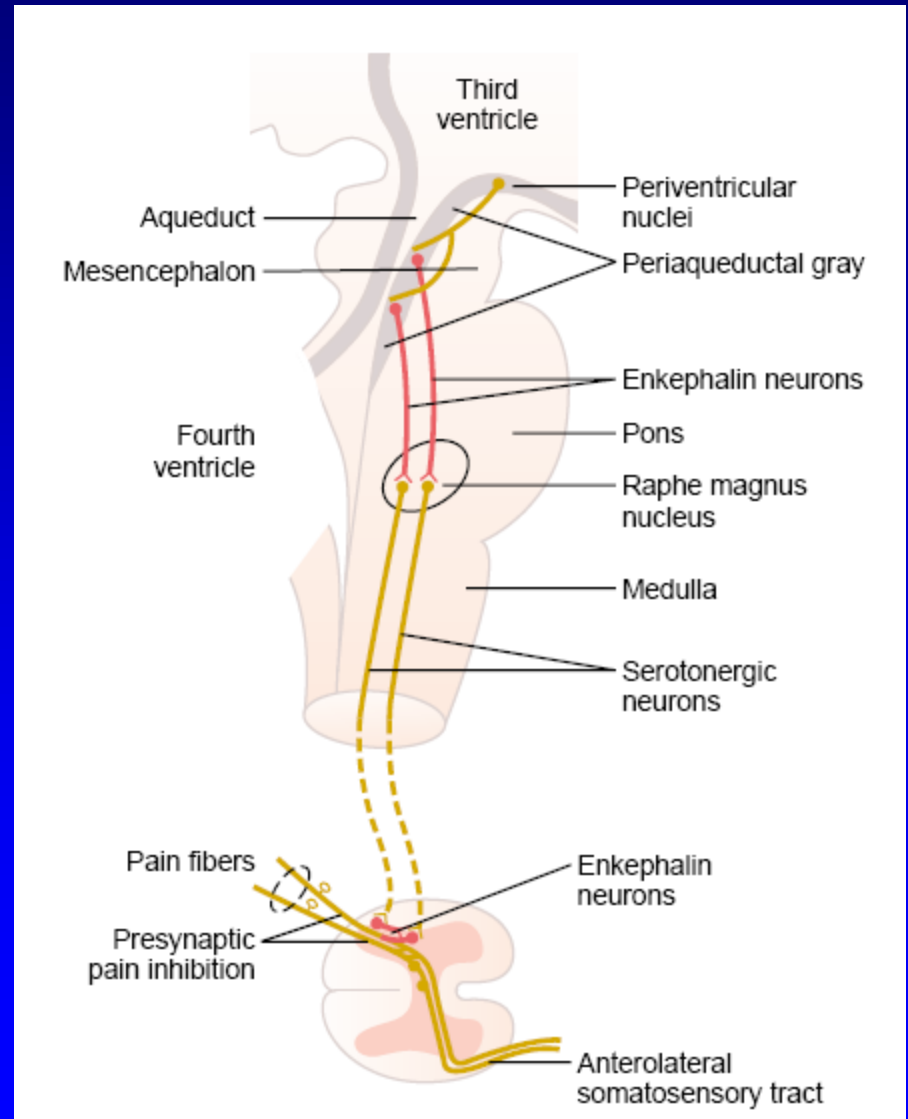
# Example of Neuropeptides

## 1) enkephalin



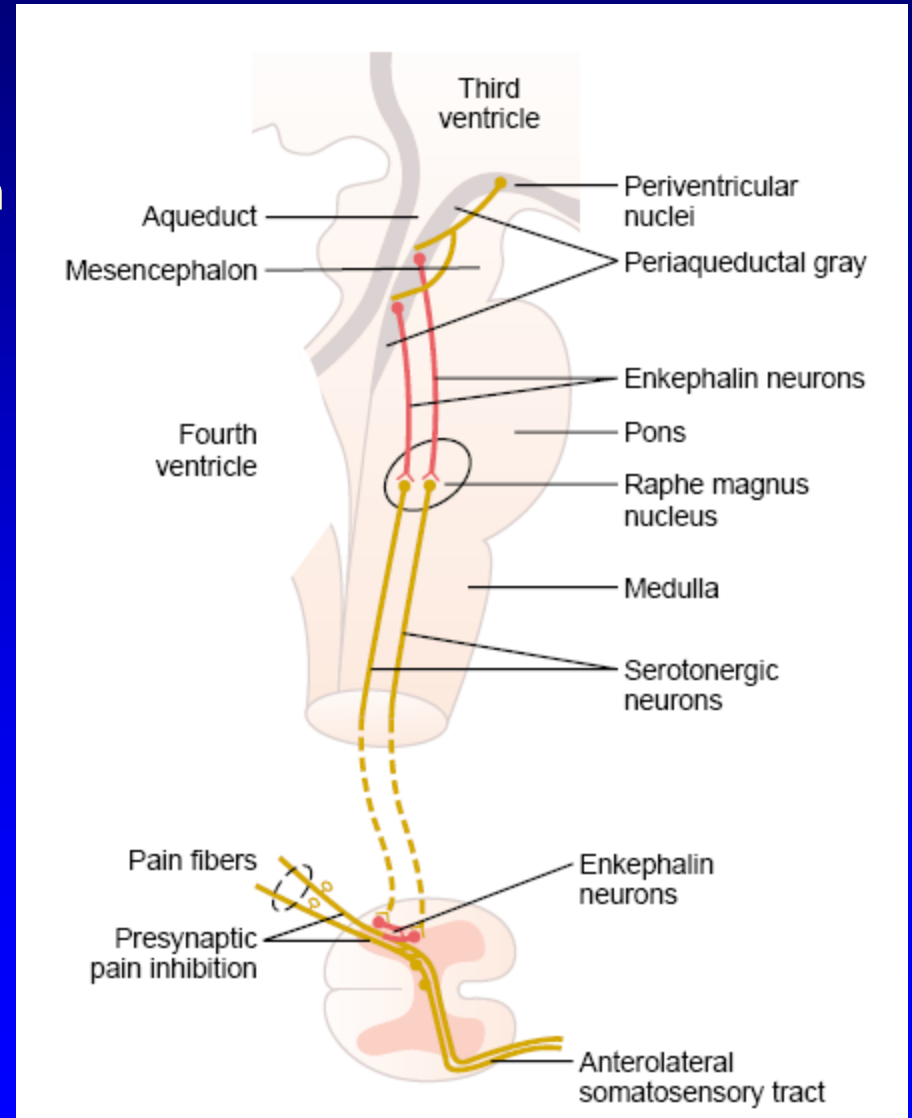
Opioid receptor :  $\delta$  receptor

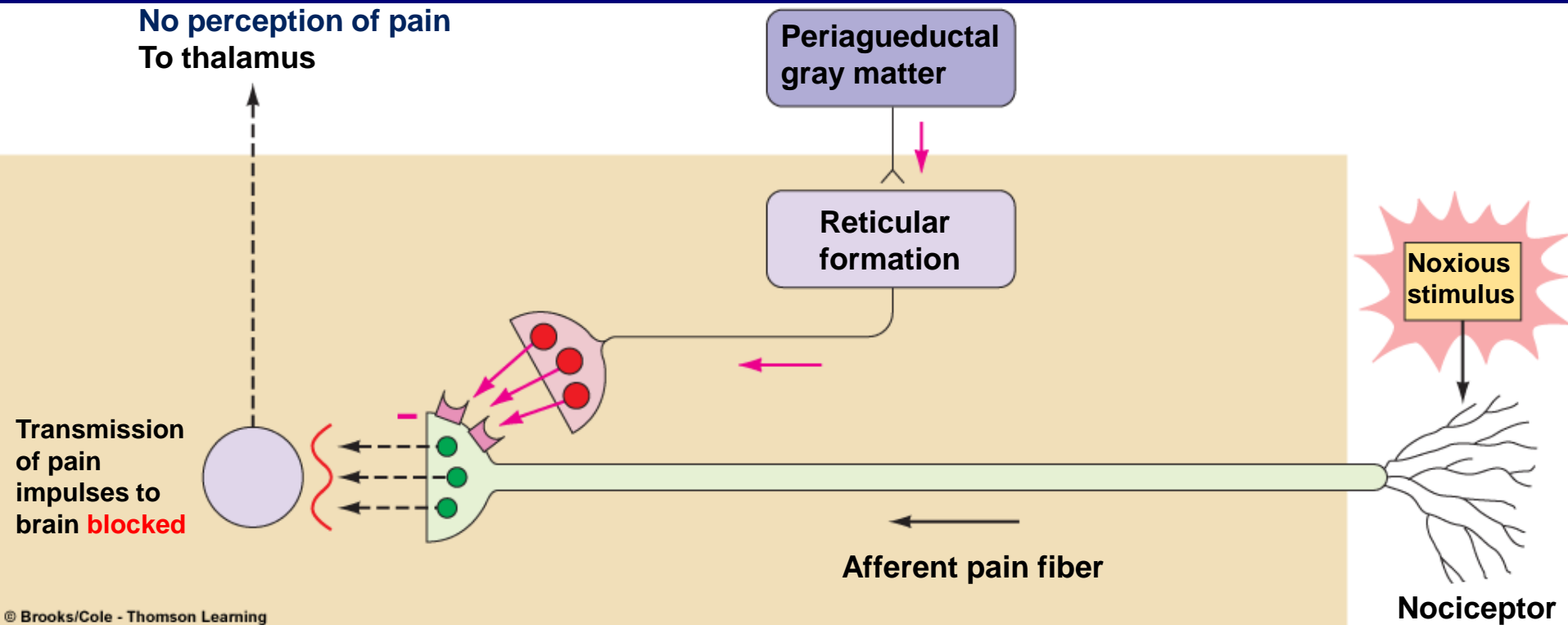
# Enkephalin pathway



# Enkephalin pathway

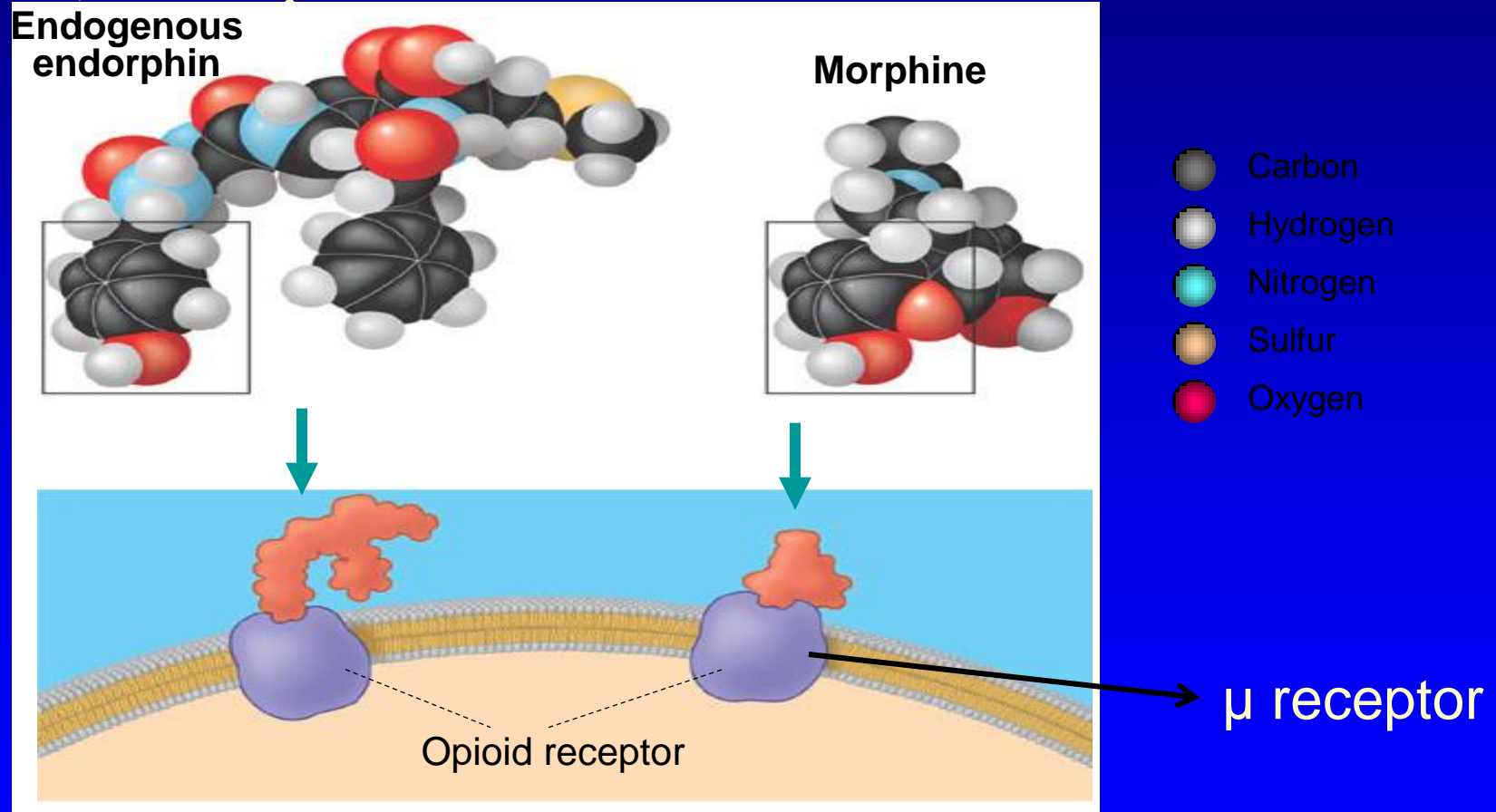
Function : analgesia by block the pain before it is relayed to the brain





# Example of Neuropeptides

## 2) Endorphins



# Endorphin location and function

---

**Cerebral cortex** - influence **mood, euphoria** and **emotional** aspect of pain

**Thalamus** – influence **poorly localized deep** pain

**Midbrain** (periaqueductal grey matter) - **modulation** of pain

**Brain stem** - **respiratory control, cough reflex, nausea/vomiting** etc.

**Hypothalamus** - **temperature** and **neuro-endocrine** function

# Non-traditional Neurotransmitters

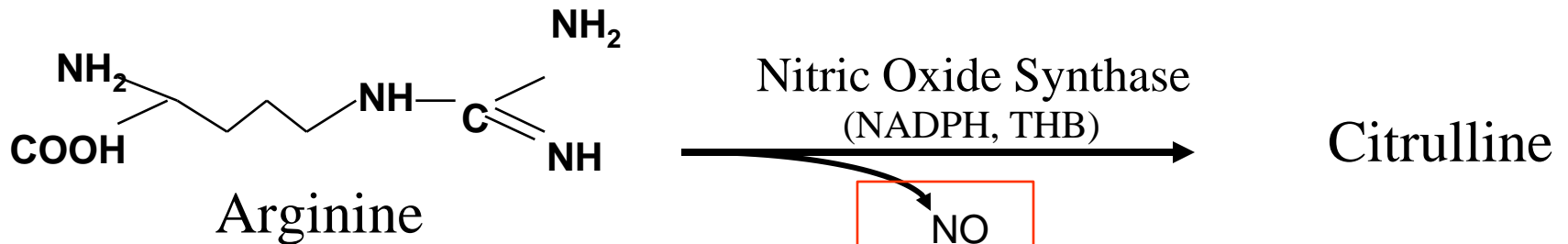
---



# Nitric Oxide

---

# Nitric Oxide



- NO is a diffusible bioactive gas produced from arginine by nitric oxide synthase

## NOS-1 (nNOS)

Constitutive  
Neuronal  
Ca<sup>++</sup> -dependent

## NOS-2 (iNOS)

Inducible  
Mostly Glial  
Ca<sup>++</sup> -independent  
Pro-inflammatory

## NOS-3 (eNOS)

Constitutive/Inducible  
Vascular endothelium  
Ca<sup>++</sup> -dependent

# Nitric Oxide (NO)

---

- NO is a diffusible bioactive gas produced from arginine by nitric oxide synthase
- NO is widely distributed in brain and peripheral tissues
- NO is not stored and synthesis is regulated by the enzyme activity

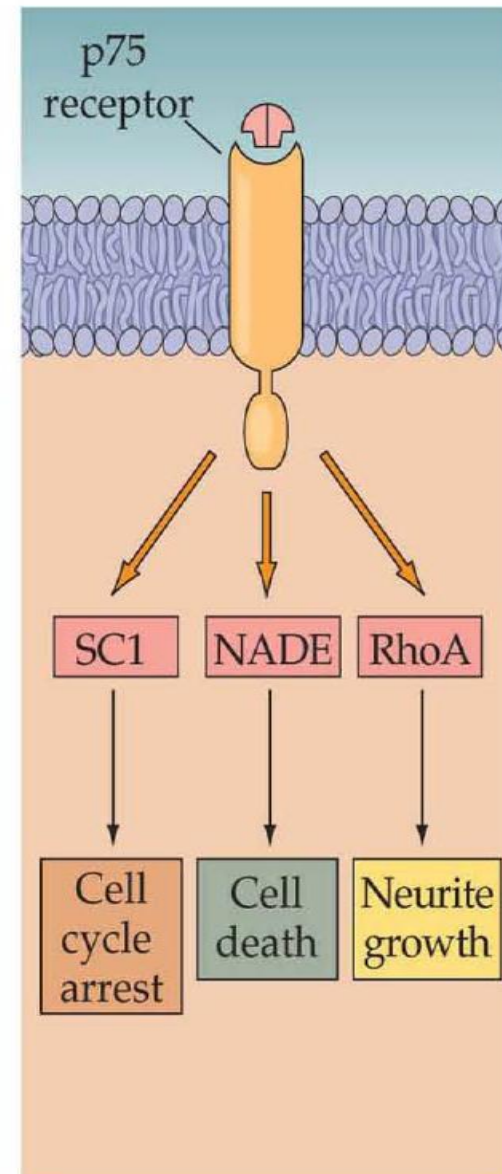
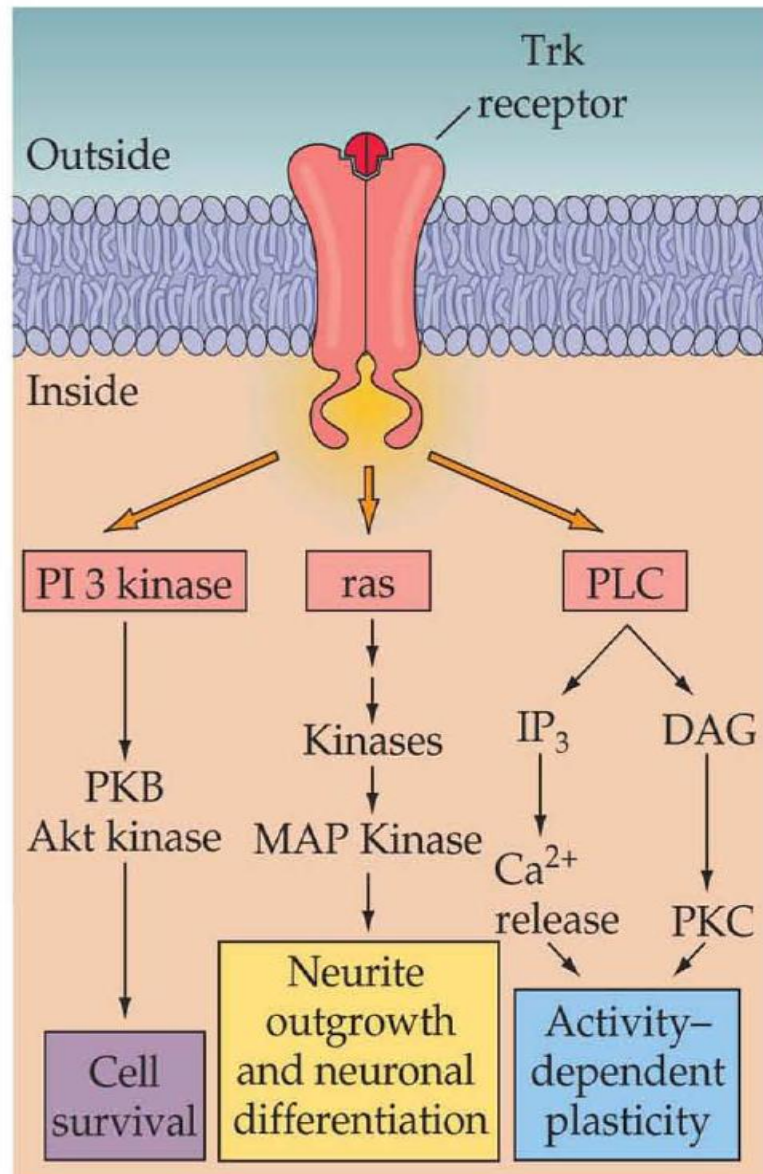
# Nitric Oxide

---

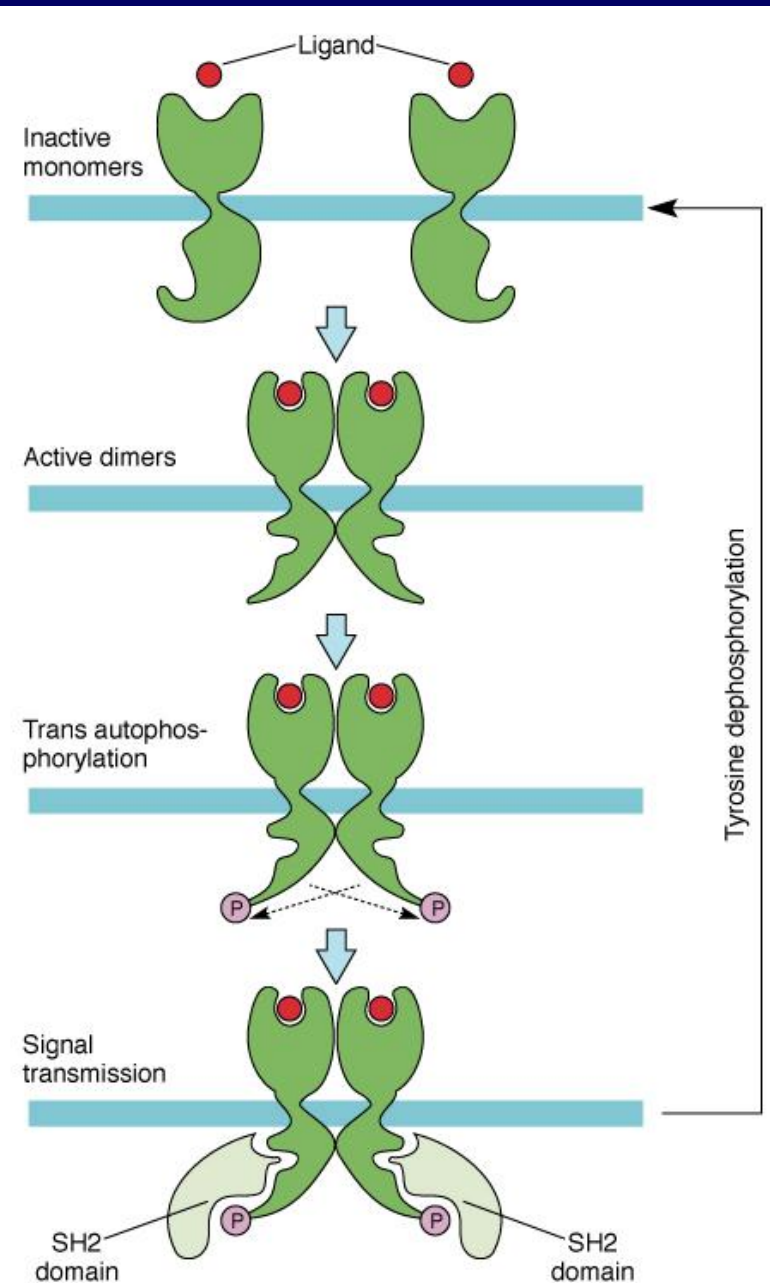
- Regulation of blood flow - Neuron-derived NO plays a major role in the regulation of blood flow, vasodilation and increased blood flow
- At the cellular level, NO can changes intracellular metabolic functions that modify neuronal excitability and influence neurotransmitter release
- In the brain, NO acts as a neuromodulator to control behavioral activity, influence memory formation, and intensify responses to painful stimuli
- May be responsible for glutamate induced neurotoxicity

# Brain-derived neurotrophic factor “BDNF”

---

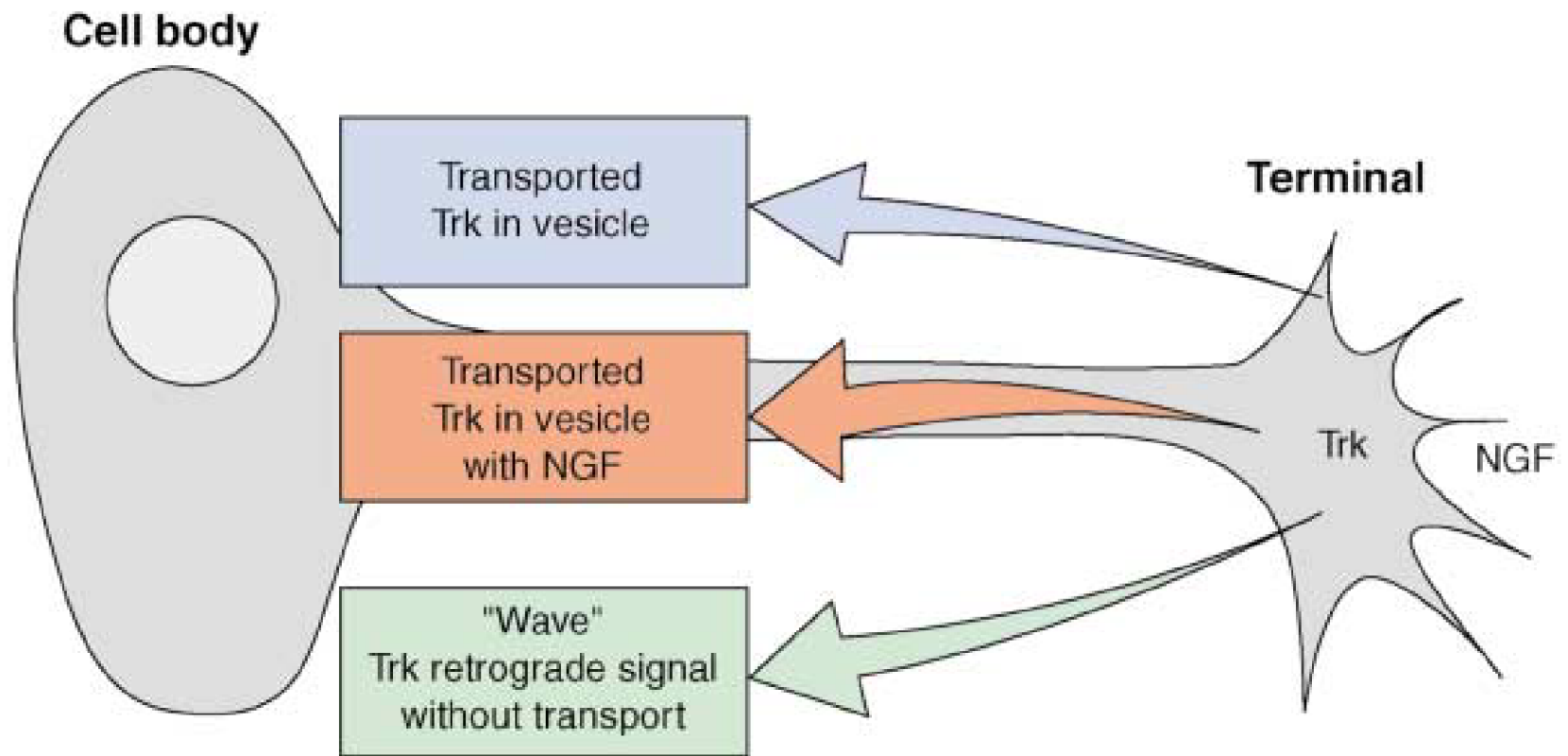


# Tyrosine kinase Receptor activation:



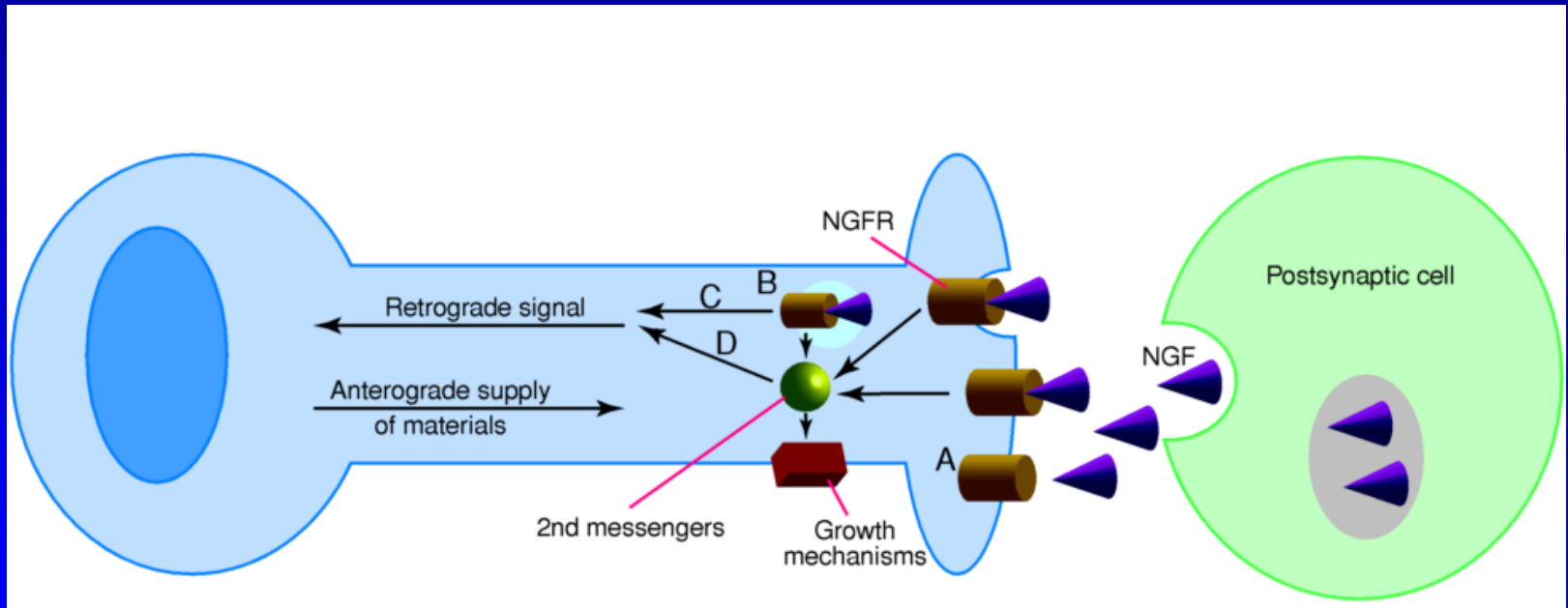
After J. Schlessinger and A. Ullrich, *Neuron* 9:384, 1992; by permission of Cell Press.  
Copyright 1999 John Wiley and Sons, Inc. All rights reserved.

Our axons can be  $>1$  m in length---how does the neurotrophin/receptor complex signal to the neuronal cell body?





# Transport of NGF



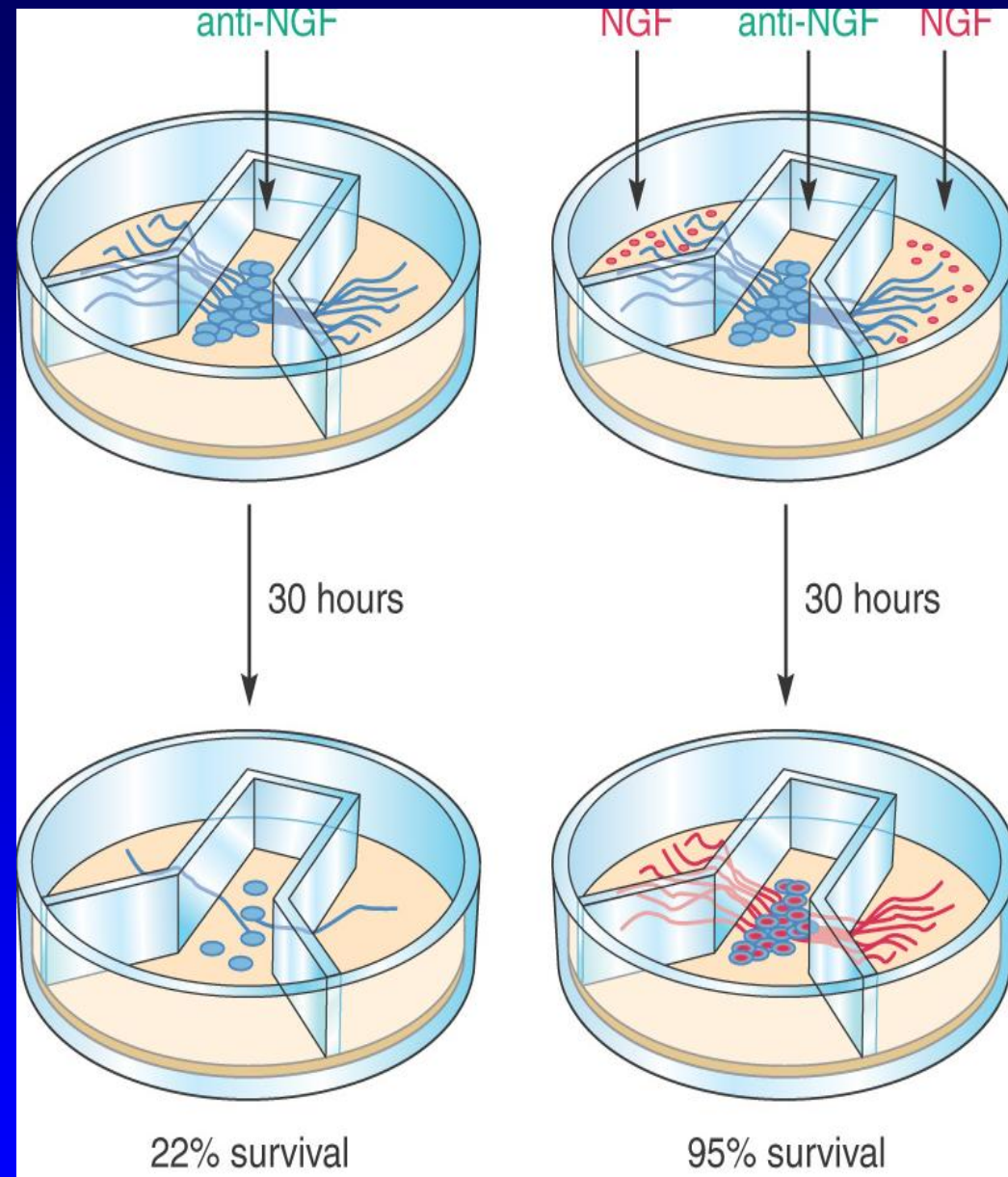
## NGF signal can be transduced at the tips of growing neuronal processes

Sympathetic neurons were placed in a TC system that allowed the somas and neurites to be bathed in different media.

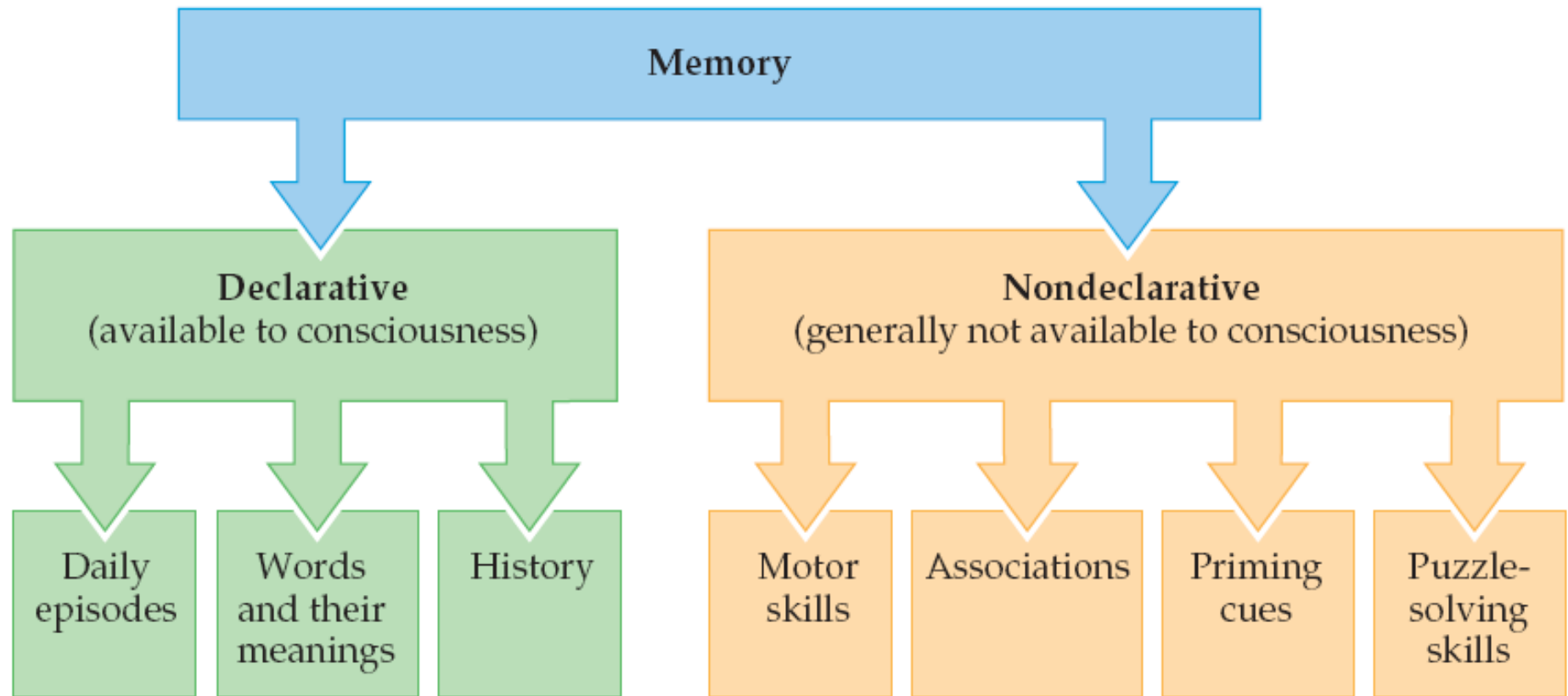
L: Most neurons die when grown without NGF for 30 hr.

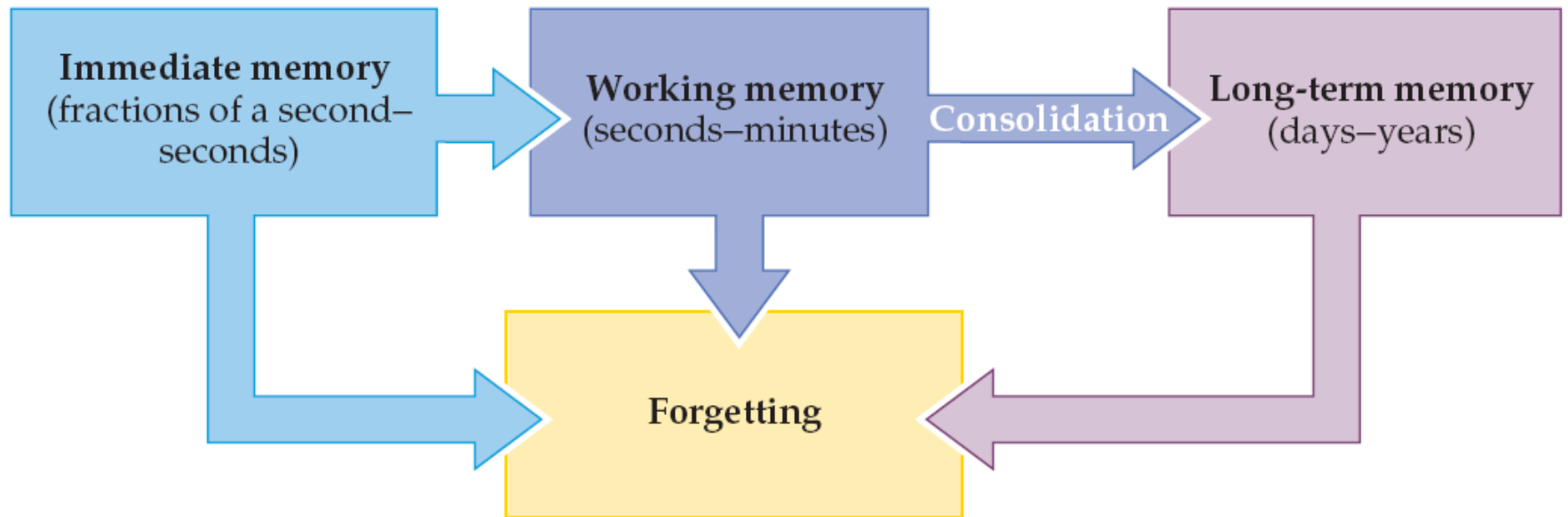
R: Neurons can be kept alive by adding NGF only to the compartments with growing neurites.

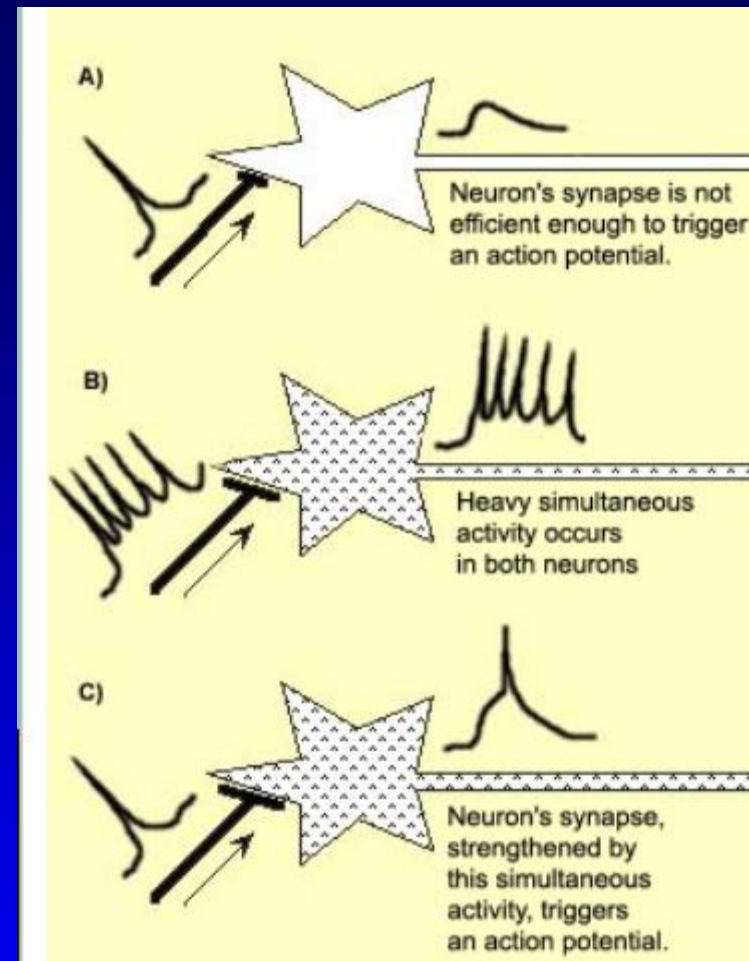
In both cases, anti-NGF prevented TrkA activation in the central compartment.



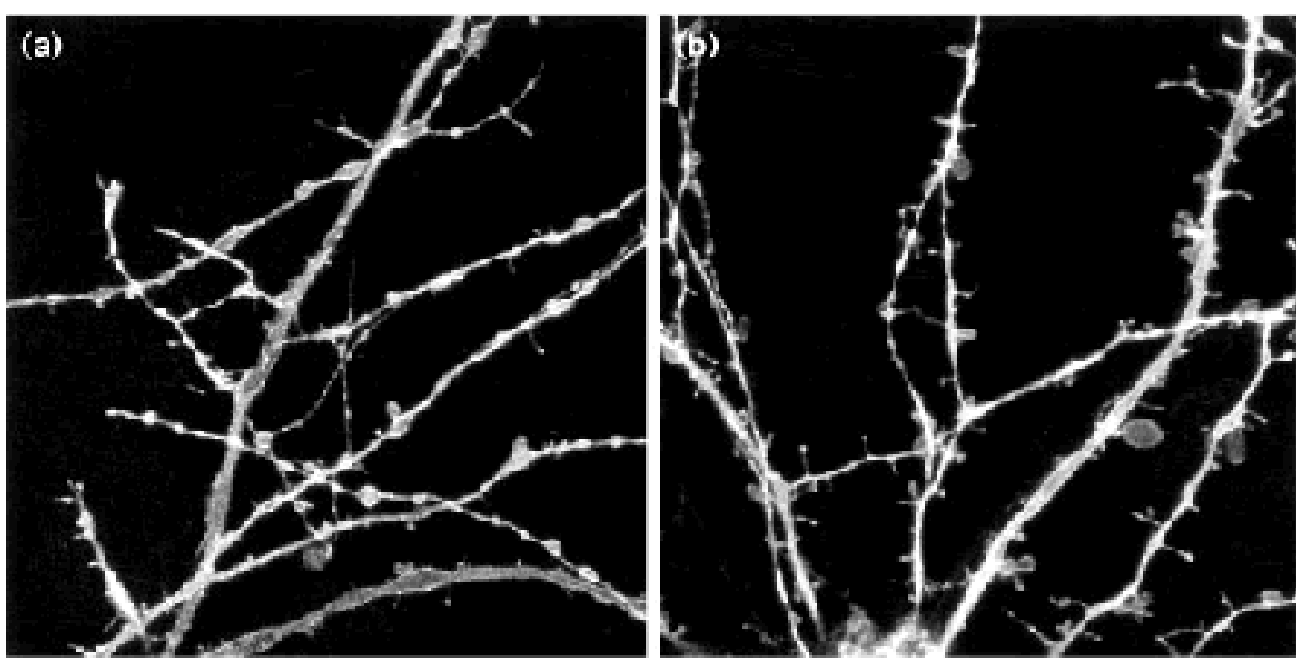
# Memory



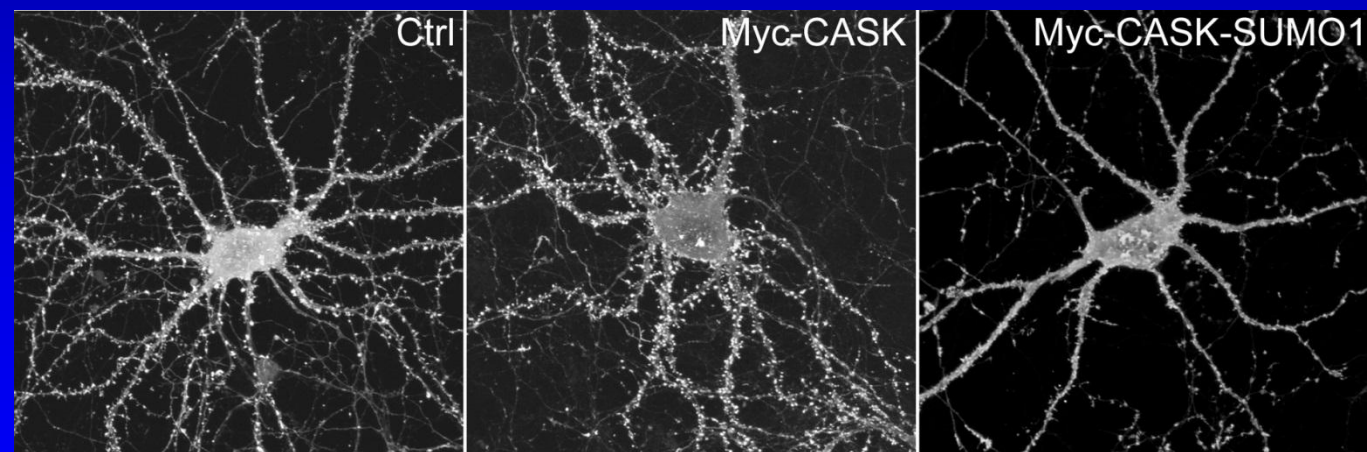


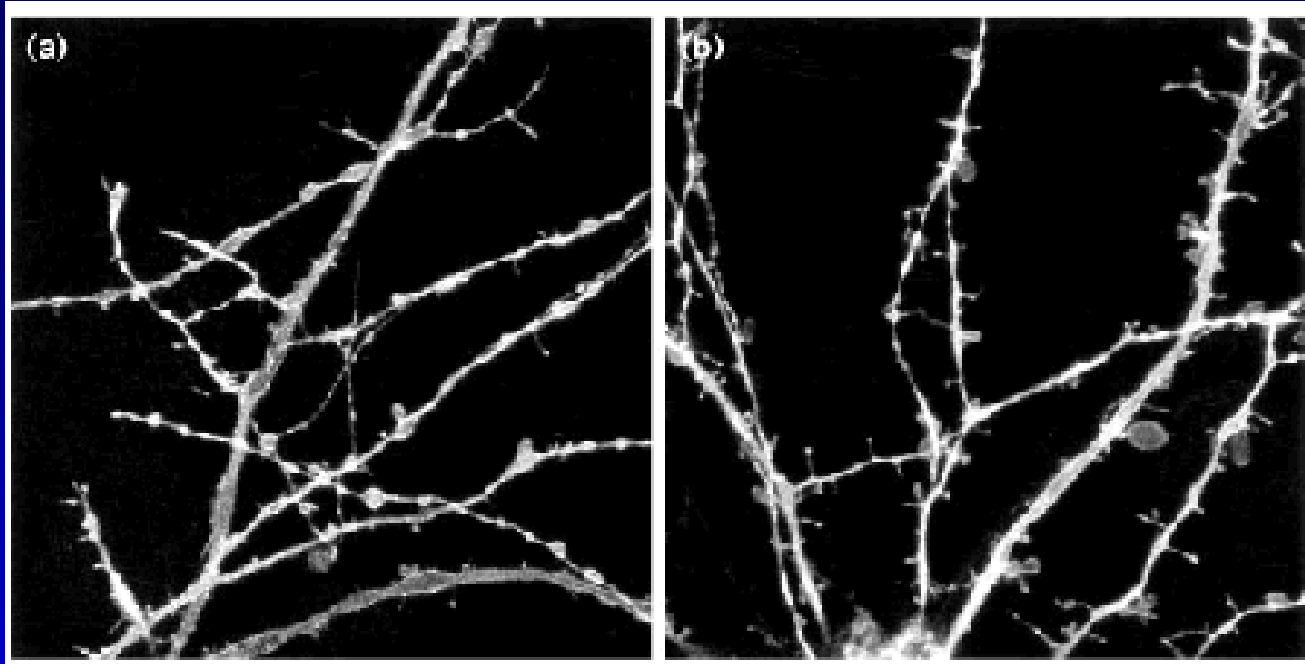


- Long term potentiation LTP , and LTD



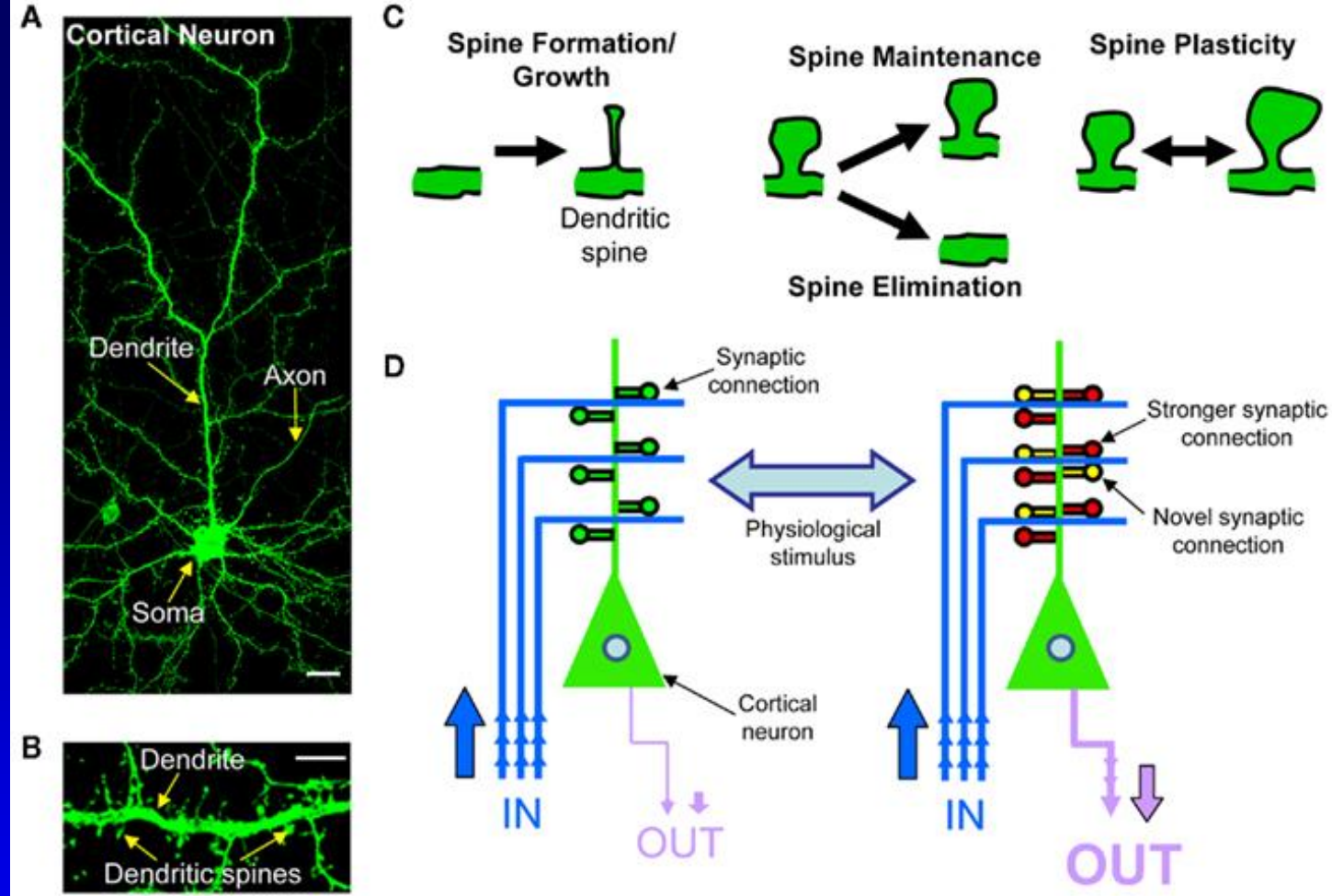
- Spines





- Spines
- Long term potentiation LTP and LTD
- The glutamate receptor (NMDA)





- Spines
- Long term potentiation LTP and LTD
- The glutamate receptor (NMDA)
- neuromodulators “NO, 5HT, norepinephrine”



**Henry Gustav Molaison (H.M.)**



- Surgical removal of left and right medial temporal lobes (hippocampus, parahippocampal gyrus)
- Anterograde amnesia

# Memory in the brain

- Cortex
- Amygdala
- Cerebellum

**Explicit Vs. implicit memory**